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ELLIPTICAL HUMAN ERYTHROCYTES

REPORT OF TWO CASES *

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The red blood cells of mammals, with the exception of one family, are circular in outline. Those of the lower vertebrates, with the exception of one family, are elliptical or oval. The one exception among the mammals is a terrestrial family, the Camelidae, the red cells of which are elliptical. The one exception among the lower vertebrates is a marine family, the Cyclostomata, the red cells of which are round. Individual variation among the cells is unusual; Ponder [1] said of the Mammalia: "The uniformity of shape met with in the red cells is very striking and in well made preparations scarcely any deformed cells will be seen."

The erythrocytes of man, aside from the poikilocytes seen in anemia, ordinarily present the form of circular, biconcave disks, whether examined in the counting chamber, in fresh blood under a coverslip or in dried films. Günther,[2] however, called attention to the fact that in dry films of human blood an occasional elliptical cell is not infrequently seen.

There are on record a few cases in man in which as large a proportion as 95 per cent of the erythrocytes have been found to be oval or elliptical instead of round. It is the object in this paper to report two instances of this anomaly and to present a report of what the writers believe to be the first autopsy in such a case.

The first case of elliptical human erythrocytes was reported by Dresbach [3] in 1904 as occurring in a healthy young student whose red blood cell count was 5,000,000 and whose hemoglobin was up to standard. Ewald, in writing to Dresbach about this case, which was the subject of considerable correspondence at the time, said that he thought that a

* Submitted for publication, Aug. 25, 1931.

* From the Edward Hines, Jr., Hospital.

1. Ponder, Eric: The Erythrocyte and the Action of Simple Hemolysins, Edinburgh, Oliver & Boyd, 1924.

2. Günther, Hans: Folia haemat. **35**:383, 1928.

3. Dresbach, Melvin: Science **19**:469, 1904.

similar observation had been made at Königsberg some twenty or thirty years before, but no record of the case could be found.[4] Eleven cases were reported in the next twenty-four years: two by Bishop,[5] one by Sydenstricker,[6] two by Huck and Bigelow,[7] five by van den Bergh[8] and one by Bernhardt.[9] The number of known cases was doubled in 1929 by Hunter and Adams,[10] who discovered twelve cases in three generations of a family of Dutch origin living in Oregon and Montana. Lawrence[11] recently reported four cases. Eight cases that have not been recorded in the literature are known to us from personal correspondence, two of them observed by Jaffe,[12] two by Sydenstricker[12] and four by van den Bergh.[12] We are also permitted to refer here and elsewhere in our paper to a forthcoming article by Cheney[12] in which he will report fourteen cases in a family group comprising forty-one persons.

Of the fifty-two instances we have thus collected, including our own and Cheney's, thirty-four were found on investigating the families of the persons concerned in the previously discovered cases. We may say, then, that the anomaly has been discovered eighteen times in twenty-seven years—or in twenty-nine years if it is remembered that while Dresbach made his report in 1904, he discovered the case in 1902—and that it has been reported by eleven observers, including Cheney, whose paper is yet to appear, and ourselves. Of the fifty-two cases, twenty-eight occurred in males and twenty-four in females; forty-six of the persons concerned were white, five were black and one was a mulatto; the ages were from 3 years to 64 years; all four blood groups were represented.

DIFFERENTIAL DIAGNOSIS

The first case reported was that of a mulatto, and for this reason several of the earlier authors have been at some pains to exclude sickle

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4. Flint, Ewing, Ehrlich, Ewald and Arneth, cited by Dresbach, Melvin: Science **21**:473, 1905.

5. Bishop, F. W.: Arch. Int. Med. **14**:388, 1914.

6. Sydenstricker, V. P.: J. A. M. A. **81**:113, 1923.

7. Huck, J. G., and Bigelow, R. M.: Bull. Johns Hopkins Hosp. **34**:390, 1923.

8. van den Bergh, A. A. H.: Arch. f. Verdauungskr. **43**:65, 1928; Deutsche med. Wchnschr. **54**:1244, 1928.

9. Bernhardt, Herman: Deutsche med. Wchnschr. **54**:987, 1928.

10. Hunter, W. C., and Adams, R. B.: Ann. Int. Med. **2**:1162, 1929.

11. Lawrence, J. S.: Am. J. M. Sc. **181**:240, 1931.

12. Jaffe, R. B.; Syndenstricker, V. P.; van den Bergh, A. A. H., and Cheney, Garnet: Personal communication.

cell anemia, remembering Herrick's article on this subject,[13] which appeared in 1910. In a few instances pernicious anemia has been considered, but only to be dismissed. In the cases that we have here enumerated, neither of these conditions, nor any other, seems to have offered any difficulty, and the point will not be dwelt on further. In well marked cases, in persons in apparent health, as most of them have been, carefully made films have sufficed for the recognition of the condition. It is evident, however, from what Hunter and Adams found, that cases may easily be missed if slides show only a small percentage of elliptical cells and no clue of heredity is at hand; in seven of eleven persons presenting the anomaly among eighteen relatives whom they examined in their case, they noted that the unusual cells were "few" or "very few."[14]

ASSOCIATED DISEASE

The associated conditions have ranged from malaise to carcinoma, and treatment, when required, has varied from the simplest medication to appendectomy, in Bishop's case, and splenectomy for hemolytic jaundice, in one of van den Bergh's. In no case has any connection been established between the associated disease and the unusual shape of the erythrocytes, and in no case has treatment changed the shape of the erythrocytes.

HEREDITY

The hereditary nature of the anomaly, suspected by Dresbach and suggested by Bishop's two patients, a man and his sister, has been fully established by Hunter and Adams' large group and by Cheney's. Both sexes have transmitted it; a generation may be skipped, as shown by Bernhardt's case in one whose father and mother had normal erythrocytes.

In five of the original eighteen observations, fourteen related persons were investigated without the discovery of an additional case (Dresbach, Sydenstricker, Bernhardt and ourselves). In six of the eighteen, it was possible to investigate a considerably larger number of relatives, and among them, as we have said, thirty-four additional cases were found (Bishop, Huck and Bigelow, van den Bergh, Hunter and Adams, Lawrence, Cheney). In the remaining seven of the eighteen, no family search was reported (van den Bergh, Jaffe, Sydenstricker, Lawrence).

13. Herrick, J. B.: Arch. Int. Med. **6**:517, 1910.

14. It may be, as van den Bergh surmised and as Günther's observation suggests, that the condition is not so rare, after all.

Four of the thirty-four cases just referred to have been discovered recently by A. A. H. van den Bergh of Utrecht,[15] who succeeded in finding, scattered all over the Netherlands, eighty relatives of A. Kl., who, together with his descendants in America, comprise the group of twelve whose cases were reported by Hunter and Adams.[10] Van den Bergh found that four of the descendants of a sister of A. Kl. have the same peculiarity of elliptical erythrocytes; two are male and two are females; among them all four blood groups are represented.

NOMENCLATURE

So far no name has been assigned to the anomaly. In the *Quarterly Cumulative Index Medicus* (**9**: 419, 1931), we find "Erythrocytes, elliptical: See Anemia, sickle-cell," to which we may reasonably object, since these conditions are not related save as heredity is a factor in both. "Ovalocytosis" has been suggested, parenthetically, by Bernhardt,[9] and van den Bergh also has used this term but, likewise, only in parenthesis as a subtitle in writing of his latest discovered cases.

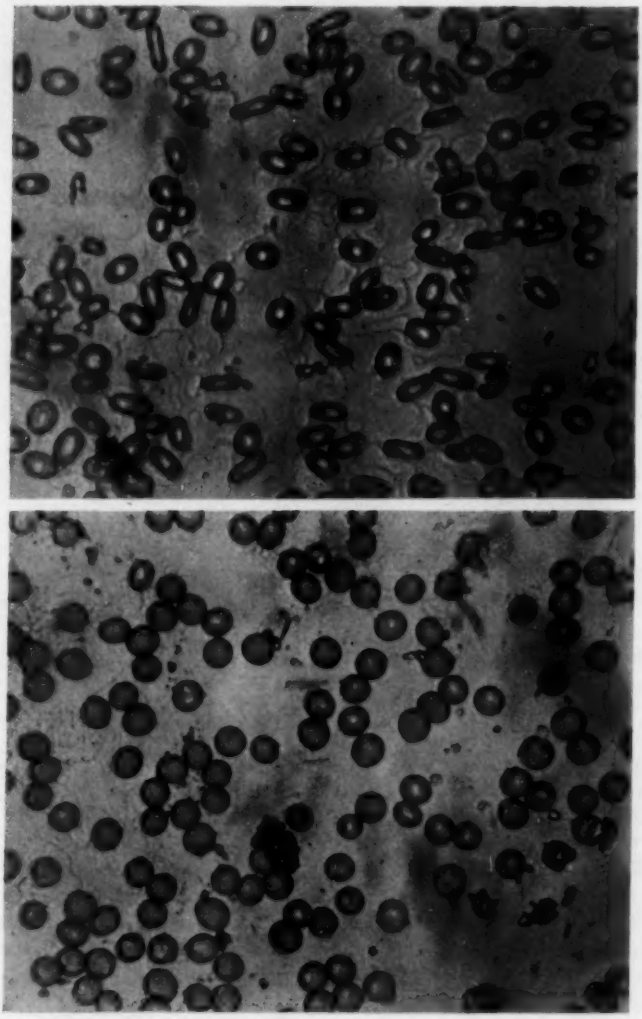
The objections to the term ovalocytosis are obvious: Not only is the word a hybrid, but it fails to indicate the erythrocyte as the cell concerned. The term ovalerythrocytosis or that of ovalerythropoiesis might be accepted, in spite of being hybrids, if it were not that the one implies an increase in the number of red cells, which is no part of the picture, while the other implies some knowledge of the process of the production of the anomalous cells, concerning which nothing is known. Since at present the condition is known only as an unexplained and unrelated morphologic peculiarity of the red blood corpuscles, it seems best to speak merely of oval or elliptical erythrocytes until such time as, happily, further knowledge may suggest a better word. "Elliptical" seems to us, from examination of our slides and from measurements made by others, somewhat the better word; it is the word used by the first two writers on the subject.

REPORT OF CASES

CASE 1.—John C., 36 years old, a colored truck driver, was admitted to the Edward Hines, Jr., Hospital, with a diagnosis of severe nephritis. His family history was unimportant. He had had measles, whooping cough and typhoid fever as a child, and gonorrhea and syphilis while he was in the army. For syphilis, he had received approximately forty injections of arsphenamine and seven of mercury. In January, 1929, he spent three weeks at the Red Cross Hospital, Louisville, Ky., because of chronic nephritis and heart trouble. He then returned to his home and worked until April when his symptoms returned. Thereafter he stayed at home until June 2, when he was admitted to this hospital.

15. van den Bergh has made a short communication on the subject to the Royal Academy of Science at Amsterdam, and his paper may be expected to appear soon. See footnote 12.

On admission, he was somewhat stuporous, but rational and able to answer questions intelligently. He became progressively worse; edema of the ankles and coarse râles at the bases of the lung appeared. On June 29, Cheyne-Stokes' breathing was present. On July 12, the patient died.



The upper photomicrograph shows oval red cells (John C.); the lower, round red cells of normal blood; Wright's stain. The two films were made on the opposite ends of the same slide, by the same person, by the same technic and at the same time.

The clinical diagnosis was: severe interstitial nephritis, with uremia; severe arterial hypertension; chronic myocarditis; aortitis, and albuminuric retinitis.

There appeared to be nothing unusual about the case until an examination of the blood was made by one of us, when it was seen that by far the greater number of the erythrocytes were elliptical instead of round.

Laboratory Findings.—During the forty days that the patient was in the hospital, the red cell count varied from 3,500,000 to 4,000,000, with a color index never less than 0.9 and never greater than 1. The ellipticity of the red corpuscles was constant. The total white cell and the differential white cell counts were normal. The reticulocyte count on one occasion was 8 per cent. The coagulation time was normal. The blood was of group A. The fragility test will be referred to later. The Wassermann test of the blood gave a negative result; the Kahn test, "one plus." Analysis of the blood showed: total nonprotein nitrogen, 41.3 mg.; urea nitrogen, 16 mg.; uric acid, 5 mg., per hundred cubic centimeters of whole blood. The van den Bergh reaction, direct and indirect, was normal. The specific gravity of the urine was from 1.010 to 1.020; a few casts were present, with a moderate number of white blood cells, an occasional red cell and albumin, urobilin and urobilinogen. The test for renal function, phenolsulphonphthalein injected intramuscularly, showed 5 per cent elimination in the first hour and 5 per cent in the second hour, a total of 10 per cent.

Autopsy.—Autopsy was performed twelve hours after death, the body remaining in the icebox meanwhile, not embalmed. The external appearance was that of a well developed, very black Negro of slender build, about 35 years old. There was moderate emaciation. The feet and ankles pitted on pressure. The hair of the head was abundant and in short tightly kinked curls. There were the normal amount and normal distribution of hair on the abdomen.

The pupils were normal. The teeth were large, white, even and unusually perfect. The face was long, oval and narrow. The cheek bones were rather prominent and the nose aquiline. There were no scars on the body, except an old scar from an operation in the groin. It was particularly noted that there were no scars or ulcers on the legs or feet.

The lungs did not meet. There was about 50 cc. of fluid in the left part of the chest and about 100 cc. in the right part. That in the right part was turbid and contained fibrinous flakes, which adhered to the visceral pleura. The left lung was somewhat compressed by the fluid in the pleural cavity and still more by the greatly enlarged heart. The lung was heavy and very wet from the contained frothy fluid. Numerous recent infarcts were present in both lobes. A few small calcified nodules were found in the upper lobe. The right lung was like the left, including infarcts, but without tuberculous nodules.

The apex of the heart was at the seventh interspace. The surface was dark, and the vessels were deeply congested. The pericardium contained a slight excess of clear fluid. Petechial hemorrhages were seen in both the inner and outer surfaces of the sac. The valves were normal. Some large antemortem clots were present. The aorta, in its first part, showed numerous yellow points, but no large plaques. The coronary arteries were normal. The heart weighed 610 Gm.

About 100 cc. of clear fluid was present in the abdomen. The stomach and the intestines, including the appendix, were apparently normal. The retroperitoneal glands were not enlarged.

On the anterior surface of the right lobe of the liver, there was a cruciform depression, the two lines of the depression being each about 2 cm. long. On section, the hepatic tissue had a nutmeg appearance. The liver weighed 1,450 Gm.

The gallbladder, the pancreas and the suprarenal glands were normal.

The spleen was small, firm and dark purple; the malpighian bodies were indistinct. The organ weighed 150 Gm.

The kidneys were small, brick red on section and granular looking. The capsule stripped with difficulty, leaving a granular surface.

The sternum, when cut into, showed a rather dry, pinkish, cancellous structure with little marrow. The ribs showed red marrow of normal appearance. In the left femur, the marrow, instead of being the usual yellow color and of thick consistency, was reddish purple and semifluid or lymphoid.

Anatomic Diagnosis.—The anatomic diagnosis was: cardiac hypertrophy and dilatation; infarction of the lung; pleurisy with effusion; old, healed pulmonary tuberculosis; chronic nephritis; chronic passive congestion of the liver, and an anomaly of the marrow of the femur.

Microscopic Examination.—Smears from the cardiac blood and from the spleen showed a predominance of oval-shaped erythrocytes. In the cardiac muscle, there was a notable increase of fibrous tissue, and elliptical erythrocytes were seen in the arterioles. The liver presented a connective tissue increase and parenchymatous changes incident to chronic passive congestion. In the kidney were marked interstitial increase of fibrous tissue, sclerosis of the blood vessels, particularly of the arterioles, and atrophy of many glomeruli. In the spleen, the connective tissue was increased, particularly about the blood vessels, and elliptical red cells were seen in the vessels. In the suprarenal glands, the blood vessels were widely dilated and full of blood, and wherever the erythrocytes were sufficiently separated, it was seen that most of them were oval instead of round. The marrow from the femurs revealed nothing significant, except an occasional oval erythrocyte. The young nucleated erythrocytes were round and in no way unusual in appearance.[16]

Three brothers, a sister and a maternal uncle of the patient were seen and all found to have normal erythrocytes. The blood group in one of the brothers was determined; it was group A.

Case 2.—J. S., 26 years old, a colored porter, had previously been in the Edward Hines, Jr., Hospital because of tricuspid disease, but at that time no note was made of any peculiarity of his erythrocytes. When readmitted on Aug. 17, 1929, he was suffering from heart failure, which increased until his death, on Feb. 28, 1930. Examination of blood film showed a high percentage of elliptical erythrocytes. The presence of this condition was confirmed by many subsequent slides and other preparations that were as convincing as those in our first case.

Autopsy showed adhesions between the pericardium, the left pleura and the posterior wall of the chest and slight nodular thickening of the edges of the mitral leaflets, the valve being of normal size. The tricuspid opening was enlarged, measuring 14 cm.

There was an excess of fluid in the pericardial sac, with fluid in the right pleural and abdominal cavities.

An 8 year old son of the patient was found to have normal erythrocytes. The blood of both the father and the son belonged to group "O."

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16. Even in the lower vertebrates, the young erythrocytes are round, the oval form being acquired only as the cell approaches maturity. See Maximow, Alexander A.: A Textbook of Histology, Philadelphia, W. B. Saunders Company, 1930, p. 61.

EXPERIMENTS AND COMMENT

Certain of our experiments have been done by all others who have had the opportunity to study similar cases. Some were designed to throw further light on the condition, and so far as we know, have not been done before. Unless otherwise indicated, the experiments described were done in the case of John C.

Experiment 1.—It was necessary to determine, first of all, if faulty technic was responsible for the unusual appearance of the erythrocytes. This was done by making many preparations from day to day with all possible care and controlling them by similar preparations of normal blood made at the same time. The result was that the more perfect the technic the more convincing was the evidence that the cells were truly elliptical, and that the less the manipulation the greater the percentage of such forms. In well made slides, the long axes of the oval cells lay in all directions and not predominantly in the direction of the smear. Most of the cells, in addition to being oval, were plainly biconcave. Deliberately faulty technic always operated to reduce the percentage of ellipses. We found, for example, that if unequal pressure was made in the preparation of dry films, some parts of the slide would show only oval cells and other parts mostly round cells; sometimes, in such a slide, groups of unusually small cells, circular in outline, were seen (fragmentation?). Our most interesting experiment of this sort consisted in putting pressure on the cover slip over a drop of blood (whole blood or oxalated or citrated blood) either before or after sealing with petrolatum. This procedure often resulted in a great reduction, sometimes in an almost complete disappearance, of oval forms, and their replacement by circular forms, some of them much smaller than normal, which did not regain their oval shape or normal size when the cover slip was gently tilted and replaced.

Experiment 2.—Was the oval shape of the erythrocytes present in the patient's circulation, or did it appear only after the blood left the vessels? The question could not be fully answered. As Ponder [1] said, no one knows the shape of human blood cells in the circulation, since there is no way of examining them within the vessels such as is afforded, for example, by the webbed foot of the frog. Our nearest approach to an answer was, perhaps, the following experiment: A drop of the patient's oxalated plasma, previously obtained, was placed on his finger, and a needle puncture was made through the drop; this was wiped off and a fresh drop of plasma applied into which a fresh drop of blood was gently squeezed. On immediate examination, practically all the cells in this preparation were oval.

Experiment 3.—Another experiment to the same end as No. 2 consisted in making a hanging drop of whole blood, sealing it and examining the erythrocytes that presently appeared in the expressed

serum as the clot formed; only oval cells appeared. Attention may be called here to the fact that at the autopsy slides made from the cardiac blood showed oval cells predominantly, and that microscopic sections showed oval cells in the splenic sinuses, capillaries of the cardiac muscle, suprarenal glands, etc.

We recall, also, that Huck and Bigelow's patient was used as a donor of blood for transfusion, and that the transfused cells kept their oval shape in the recipient's blood for a considerable time, as we infer from their statement that "no oval cells could be found after a period of two months."

Experiment 4.—Is the oval shape inherent and structural, or does it depend on some peculiarity of the patient's plasma? We did what others have done, placing washed cells from our patient in the serum of a normal person whose blood was of the same group, and this person's cells in our patient's serum. We found, as have others in like cases, that no change in the shape of the cells occurred in either preparation.

It seems clear that the peculiar shape depends on structure, a conclusion that scarcely requires experimental support, since in all reported cases both round and oval forms are found in the same environment, namely, the peripheral circulation. It must be remembered that no one has reported a case of 100 per cent elliptical erythrocytes. Why certain cells, sometimes only a few and sometimes almost all, are destined to take the oval shape, and where this shape is first assumed, are matters of which we remain ignorant. Puncture of the sternum by Bernhardt and by Cheney and our own examination of marrow from a femur have failed to show any site of origin of oval cells as such. Bernhardt's conclusion was that such cells appear first in the peripheral circulation. We, however, have been able to show that they are present in capillaries of the cardiac muscle, spleen and suprarenal glands.

In this connection, Bernhardt [9] made the following remark, which we consider valuable: "Clinically one must segregate this ovalocytosis from other clinical findings . . . and look upon it as an anomaly, a sort of atavism." This thought must have occurred to others who have encountered these extraordinary cases of oval erythrocytes in man; they seem to us as suggestive of atavism as the cases, also rare, of persistent branchial cleft.

At one time in the consideration of our first case, we thought that not only the oval shape of our patient's erythrocytes but also his blood group might be reminiscent of an ancient condition. Our patient's blood belonged to group A and the blood in all other cases in which the point was determined belonged to that group so far as we could determine at the time, a group that there is some reason for thinking was the

earliest mutation from group O, regarded by most writers as the original human group. But the blood of our second patient belonged to group O, and, as we now know from Hunter and Adams' cases and from Cheney's, all groups are represented. Nevertheless, we allow our far-fetched speculation to stand, thinking that these cases may yet, from one or the other approach, furnish a link between the marine vertebrates and man. The total number of known cases of elliptical erythrocytes in man is too small, even if the persons concerned and all their available relatives were investigated, to give us more than an intimation of a correlation between blood group and oval cell if such exists. The number of studies of three generations is only two, and these studies have not been complete, so far as we know, with respect to the blood groups.

Hetero-agglutination tests between man and other animals may in time throw some light on the subject. They have not yet been carried far, though, as Synder [17] said, a wide field is open here for the study of taxonomic relationships. Two recorded observations we here set down: 1. Landsteiner and Miller [18] reported that fourteen of seventeen chimpanzees examined had blood belonging to group A. 2. Karshner [19] found that human serum of group A seldom agglutinated the oval cells of the chicken—only eight times in 169 tests—while serum of group B never failed to agglutinate in 112 tests.

That even morphologic studies might lead to some clue or at least disclose some interesting and curious facts, if animal hematology were given the same intensive study that human hematology has received in the last fifteen years, is suggested by a paragraph that we find in an old journal wherein the author,[20] referring to the red cells of Mexican and Persian deer, spoke as follows: ". . . curved and gibbous in the middle and acutely pointed at the ends, with a concave and convex margin, like a crescent"—quite a number of such forms being present aside from the usual disks.

Does the occurrence of elliptical erythrocytes in man throw any light on the question, long debated, whether the human erythrocyte in its usual form is a cell the shape of which is maintained by a special structure, as Ponder [21] believes, or merely a fluid droplet the form of which is due to surface forces only, as maintained by Norris, Gough,[22] and

17. Snyder, L. H.: Blood Grouping, Baltimore, Williams & Wilkins Company, 1929, p. 116.

18. Landsteiner, K., and Miller, C. P.: J. Exper. Med. **43**:860, 1925.

19. Karshner, W. M.: J. Lab. & Clin. Med. **14**:346, 1929.

20. Gulliver, George: Abstr. Philos. Tr. Roy. Soc. London **4**:199, 1840; London & Edinburgh Philos. Mag., November, 1840, p. 329.

21. Ponder, Eric: Quart. J. Exper. Physiol. **14**:338, 1924.

22. Gough, Alfred: Biochem. J. **18**:202, 1923.

others? We think it suggests a probability of the correctness of Ponder's view. We have presented evidence to show that the elliptical human erythrocyte is such by structure, and that it is a functionally normal cell in normal, though exceptional, human beings—in other words that there are normal human erythrocytes the shape of which is due to structure.

If the usual, biconcave, disk-shaped erythrocyte is likewise such by structure, it would seem to be of simpler architecture than the biconcave oval and at the same time more efficient and more economical, as has been shown mathematically, for its principal function of oxygen transport and exchange. Here, again, one may guess that the elliptical human erythrocyte is an atavistic form, structurally such from some early necessity (say a theoretically less constant plasma), while the usual disk in man and most of the higher vertebrates is a later development adapted to conditions (say a fully evolved, species-specific plasma) in which such a degree of stability or rigidity of form is no longer necessary or advantageous. One sees a somewhat similar adaptation of cells and serum, still in progress and not yet completed, in the blood of the new-born child—not in any changing structure in the erythrocyte, but in the shifting relative strength of receptors in cells and serum, in neither of which is development likely to be complete at birth, at which time there is usually a relatively strong receptor development in the serum and a weak receptor development in the cell—plainly a temporary defensive mechanism without which antibodies in the maternal circulation might be bound on the erythrocytes of the child; a mechanism that continues for some time beyond its apparent usefulness until, some months after birth, permanent relations are attained between cells and serum and the blood group is established. Whether this stability is attained first in the cells or in the serum is not known. The matter is discussed by Thomsen [23] in an article on the quantitative development of group-specific substances in the serum of the new-born infant.

Experiment 5.—Sealed wet preparations were made (1) from fresh blood and (2) from citrated or oxalated blood and kept for long periods both at room temperature and in the icebox. Neither a reduction in the number of the oval cells nor any change in their shape was seen in any of these preparations in twenty-four hours; later, beginning as a rule in seventy-two hours, many of the cells became circular in outline. To establish this observation, we kept a fresh, wet, sealed preparation on the microscope stage unmoved for ninety-six hours. The change to round form that we speak of occurred much later in preparations kept in the icebox, beginning on the thirteenth day.

23. Thomsen, Oluf: Ztschr. f. Immunitätsforsch. u. exper. Therap. **71**:199, 1931.

Experiment 6.—Blood from the finger or from the ear was collected in capillary tubes about 15 cm. long, and the ends of the tubes were sealed. In these tubes, the blood clotted in a long thread, which could be drawn out when the tube was opened. In the remaining serum, which could then be blown out, erythrocytes could always be found. Gram [24] recommended this method for the preservation of cells for examination over long periods. We sent such tubes as far away as the Pacific coast, and we were told that on the arrival of the tubes there, oval cells were found in the serum.

Experiment 7.—We confirmed Bernhardt's observation [9] that in beginning hemolysis in hypotonic salt solution some of the oval cells take on the round form. But we can add that if the process is watched under the microscope, many oval shadows will be seen—oval cells that undergo hemolysis without change in shape. Some, too, if the cells are in motion, may be seen to lose their biconcavity and become flimsy, bending double and flattening out again while keeping their oval outline.

Experiment 8.—A change of shape from oval to round can take place, without hemolysis, as we showed in our first experiment. It can also take place, without hemolysis, under another condition: When the blood of our patient was repeatedly washed with isotonic salt solution and the sediment finally suspended in salt solution, it was found that the oval cells had largely disappeared and been replaced by round forms. In this respect, we think the oval cells behaved like the usual normal discoid human erythrocytes, which, as Gough [22] observed, confirmed by Ponder,[21] change to spheres when immersed in salt solution. Kanellis [25] showed that experimentally the poikilocytes in pernicious anemia are not changed in shape by washing with hypotonic, hypertonic or isotonic salt solution. We made a somewhat similar experiment in a case of profound secondary anemia (C. B., gastric carcinoma) and saw no change in the poikilocytes. This adds somewhat to the evidence that the oval erythrocyte is not a poikilocyte due primarily or secondarily to any disease, but is a congenital anomaly not incompatible with health.

Experiment 9.—On two occasions, our patient was given oxygen by means of the apparatus for measuring basal metabolism; the inhalation of oxygen made no change in the shape of his red cells.

Experiment 10.—Under the conditions of experiment 10 which we repeated several times, some cells may have changed from oval to

24. Gram, H. C., quoted by Holler, G., and Kudela, O.: Folia haemat. **35**:97, 1928.

25. Kanellis, E.: Folia haemat. **35**: 71, 1928.

round, but we doubt if this fully explains the findings that we are about to record:

1. The patient's blood was collected in citrated isotonic salt solution and mixed by inverting the tube a few times without shaking; then it was centrifugated at low speed for two minutes. Wet sealed preparations were then made both from the upper part of the tube and from the bottom. The former showed mostly round cells; the latter, almost nothing but ovals.

2. Blood was taken from a vein into an excess of citrated salt solution and gently mixed. After standing an hour, a large proportion of the cells in the upper part of the tube were round, while most of those at the bottom were oval. The supernatant layer was then decanted into a second tube, and the two tubes were left standing over night. Next day the sediment of cells in the first tube still showed almost none but oval cells; no hemolysis had occurred in either tube. The second tube was gently shaken to bring the cells into suspension again and then centrifugated briefly at low speed until a partial clearing of the upper layer was seen. In the preparations from the upper portion, we found that 90 per cent of the cells were round. The contents were then decanted down to the last half cubic centimeter, and this sediment was found to be composed almost wholly of oval cells.

We could hardly escape the conclusion that both oval and round cells were present in our patient's circulation, and that the oval cells were the heavier.

Experiment 11.—Fragility of the erythrocytes was normal in cases reported by Huck and Bigelow, Bernhardt and Cheney. Our two cases call for some comment.

In the case of John C., hemolysis began at 0.5 per cent and was complete at 0.22 per cent, which is to be compared with 0.42 per cent and 0.32 per cent for the normal control done at the same time. In the case of J. S., hemolysis began in the test and the control at the same point, viz., 0.46 per cent, but the end-points were far apart—0.24 per cent for the patient and 0.36 per cent for the control done at the same time. In the case of J. S., we effected a separation of the round and the oval cells in the manner described, and repeated the test on the two fractions, the suspensions being first standardized as to opacity. The result was that cells from the upper layer (mostly round) agreed with the control in the point of beginning hemolysis (0.46 per cent), but went a little farther to the end-point, which was 0.32 per cent; whereas cells from the bottom of the tube (mostly oval) did not begin to hemolyze short of 0.42 per cent and were not completely hemolyzed short of 0.24 per cent, the end-point agreeing, as may be seen, with that of the patient's whole blood. When the like experiment was done

with normal blood, the fragility of the cells from the upper layer was identical with that of the cells from the bottom of the tube.

In both of our patients, therefore, some of the erythrocytes appeared to be less resistant and some more resistant than the whole blood of the controls, and in the case of J. S. we were able to show that the cells that were the more resistant were the oval cells.

SUMMARY

Fifty-two instances of elliptical human erythrocytes are collected, including two of our own. An analysis of the cases establishes the condition as a hereditary anomaly not incompatible with health and without any proved relation to disease, occurring in whites, blacks and mulattos, and about equally divided between males and females. Both sexes may transmit it. A generation may be skipped. All four blood groups are represented.

An autopsy is reported showing that oval cells were present in the smallest vessels of the cardiac muscle, spleen and suprarenal glands. An occasional oval erythrocyte was found in the marrow of the femur, and the marrow there, instead of having the usual yellow color and thick consistency, was reddish purple and semifluid or lymphoid. In other respects, the autopsy disclosed nothing more than was anticipated from the patient's clinical condition, which was chiefly that of severe nephritis.

Certain experiments are presented and discussed. Some of them were merely such as were necessary to establish the validity of the cases reported. Others yielded the following observations: 1. When the blood of one of the patients was subjected to the action of hypotonic salt solution, the oval cells resembled in their behavior normal erythrocytes rather than the poikilocytes of a patient with anemia 2. Both round and oval cells were shown to exist together in the peripheral circulation, and the oval shape was shown to depend on structure and not on environment. 3. It was found possible to separate the two kinds of cells and to do certain experiments that showed that the oval cells were heavier than the round cells, and that they were more resistant than the round cells to the hemolytic action of hypotonic salt solution.

A speculation is offered as to the possible atavistic significance of the occurrence of elliptical erythrocytes in man.

LESIONS OF THE NERVOUS SYSTEM RESULTING FROM DEFICIENCY OF THE VITAMIN B COMPLEX*

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It has been known for a long time that deficiency of vitamin B [1] leads to well defined neuromuscular symptoms. In animals, these are manifested as spastic paralysis, ataxia, opisthotonus and convulsions. In 1897, Eijkman [2] described noninflammatory atrophic degeneration of the medullary sheaths of the nerves in hens fed on a diet of polished rice. He also noted chromatolysis and atrophy of the ganglion cells of the anterior horns of the spinal cord. Vedder and Clark [3] in 1912 made similar observations in rice-fed fowls. They found, in addition, chromatolysis in the dorsal and ventral root ganglions and degeneration in the nerve roots and spinal cord involving the myelin sheaths and axis cylinders. Pigeons fed on autoclaved rice were found by McCarrison [4] to have degenerated fibers throughout the spinal cord and in the nerve roots. Furthermore, the sciatic nerves in his animals showed degenerated fibers in 88 per cent of the cases, and the vagus nerves in about 63 per cent. He concluded that the paralytic symptoms were due mainly to impaired functional activity of nerve cells and much more rarely to their degeneration. Findlay,[5] in an experimental study on avian beriberi, found a complete disappearance of the Nissl

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1. In this paper, the term vitamin B refers to the mixture of water-soluble vitamins composed of the heat-labile antineuritic factor (vitamin B_1) and the heat-stable pellagra-preventive factor (vitamin B_2). The terms vitamin B_2 and vitamin G are used synonymously.

2. Eijkman, C.: Eine Beri Beri-Ähnliche Krankheit der Hühner, Virchows Arch. f. path. Anat. **148**:523, 1897.

3. Vedder, E. B., and Clark, E.: A Study of Polyneuritis Gallinarum: A Fifth Contribution to the Etiology of Beriberi, Philippine J. Sc. **7B**:423, 1912.

4. McCarrison, R.: The Pathogenesis of Deficiency Disease, Indian J. M. Research **6**: 275, 1919.

5. Findlay, G. M.: An Experimental Study of Avian Beriberi, J. Path. & Bact. **24**:175, 1921.

bodies in the nerve cells of the spinal cord and evidence of nuclear degeneration and myelin disintegration in the sciatic and vagus nerves. He stated that in two pigeons that died of chronic inanition demyelination was present in the sciatic nerves.

The first work of importance conducted on mammals was that of Voegtlin and Lake,[6] who produced polyneuritis in cats by feeding alkali-treated, autoclaved meat. The changes that they observed consisted of myelin degeneration of the sciatic nerves similar to polyneuritis gallinarum, and of degenerated fibers at all levels of the spinal cord.

It is difficult to attribute the changes described in the early work solely to lack of the antineuritic vitamin, owing to the fact that the rations used in these experiments were deficient in more than one essential nutrient, namely, protein (rice diets), minerals and other vitamins. The animals were therefore suffering from multiple dietary deficiencies.

Later investigations on this question have limited the regimen more definitely to lack of vitamin B alone. It is a well known fact that the absence of this vitamin leads to a loss of appetite and consequently to voluntary starvation (Cowgill[7]). This factor was taken into consideration by Woollard,[8] who adequately controlled the effects of inanition. In rats fed an artificial diet complete so far as known except with respect to undifferentiated vitamin B, he found changes in the intermuscular medullated motor and sensory nerves and their endings. In the control animals, totally deprived of food but receiving a sufficient amount of autolyzed yeast, similar but less extensive changes were observed.

In recent years it has been found that what has hitherto been called vitamin B_1 is really a mixture of at least two components, namely, the heat-labile antineuritic factor and a thermostable substance, the absence of which is thought to produce pellagra (Goldberger and others,[9] Chick and Roscoe[10]). Stern and Findlay[11] studied the changes in the nervous

6. Voegtlin, C., and Lake, G. C.: Experimental Mammalian Polyneuritis Produced by a Deficient Diet, Am. J. Physiol. **47**: 558, 1919.

7. Cowgill, G. R.: A Contribution to the Study of the Relation Between Vitamin-B and the Nutrition of the Dog, Am. J. Physiol. **57**:420, 1921.

8. Woollard, H. H.: The Nature of the Structural Changes in Nerve Endings in Starvation and in Beriberi, J. Anat. **61**:283, 1927.

9. Goldberger, J.; Wheeler, G. A.; Lillie, R. D., and Rogers, L. M.: Experimental Black Tongue and the Black Tongue Preventive Action in Yeast, Pub. Health Rep. **43**:657, 1928.

10. Chick, H., and Roscoe, M. H.: The Dual Nature of Water-Soluble Vitamin B, Biochem. J. **22**:790, 1928.

11. Stern, R. O., and Findlay, M.: The Nervous System in Rats Fed on Diets Deficient in Vitamins B_1 and B_2, J. Path. & Bact. **32**:63, 1929.

system of rats fed diets deficient in vitamin B_1 (antineuritic component) and B_2 (pellagra-preventive factor), respectively. In the first group of animals, they found chromatolytic changes in the ganglion cells of the spinal cord and early degeneration of the myelin of the peripheral nerves. In the second group, the changes consisted of swelling and vacuolization of the anterior horn cells of the spinal cord with the deposition in them of lipochrome pigment.

Gildea, Kattwinkel and Castle [12] attempted to correlate the clinical manifestations of deficiency of the B factors with anatomic alterations of the nervous system commonly noted in pernicious anemia. For this purpose, they used dogs that were fed the Cowgill diet [13] and described lesions in the cords of these animals that resembled those seen in so-called combined system disease.

The majority of the investigators in this field heretofore have utilized the pigeon or the rat as the experimental animal. No complete investigation of the nervous system, peripheral as well as central, has been conducted on the dog. In view of the extensive work done on this animal by Cowgill and by Goldberger in their studies on the relation of the water-soluble B vitamins to nutritional disease, it appeared to be of interest to see whether the anatomic basis for the clinical manifestations observed in the dog was similar to that already described in the other species. Because it had been claimed by Marrian, Baker, Drummond and Woollard [14] that the disorders found in B-avitaminosis are due entirely to the accompanying factor of inanition, and because these investigators had described a peripheral polyneuritis in rats deprived of food completely, it was important to study further the rôle of inanition in producing these anatomic lesions.

EXPERIMENTAL PROCEDURE

Diets Employed.—Five of the twelve animals used in this study were allowed to subsist from the beginning of the experiment on the artificial diet described by Cowgill,[13] supplemented, however, with 0.3 cc. of cod liver oil per kilogram per day. The composition of the ration is shown in table 1.

It should be pointed out that although this diet is deficient in the vitamin B complex, the changes observed in the study here reported are related essentially to lack of the antineuritic component. The ration is low in its content of the heat-stable B_2 substance, but not altogether devoid of it. The commercial casein

12. Gildea, E. F.; Kattwinkel, E. E., and Castle, W. B.: Experimental Combined System Disease, New England J. Med. **202**:523, 1930.

13. Cowgill, G. R.: Studies in the Physiology of Vitamins, Am. J. Physiol. **66**:164, 1923.

14. Marrian, G. F.; Baker, L. C.; Drummond, J. C., and Woollard, H. H.: Physiological Rôle of Vitamin B: Relation of Inanition to Vitamin B Deficiency in Pigeons, Biochem. J. **21**:1336, 1927.

employed was shown by Evans and Burr [15] to contain an appreciable amount of the thermostable vitamin (B_2). How effective small amounts of the missing essential, when taken daily in the diet, may be in delaying symptoms of a deficiency disease is demonstrated by the experiments of Goldberger and his collaborators,[16] in which they observed that increase in the amount of acid-leached casein in the diet suspended considerably the onset of the symptoms of B_2-deficiency in dogs. As the casein used in the diet here described was not further purified by acidulated water extraction, as was done in the experiments of Goldberger and his associates, the ration must have carried a significantly greater amount of the B_2 factor. Furthermore, the time required for the development of pellagra-like manifestations is usually longer than that found necessary for the production of polyneuritis. These studies were carried to the point at which neuritic symptoms occurred, at which

TABLE 1.—*Casein III Diet*

	Per Cent	Calories
Casein, commercial (81.9 per cent protein)	41.2	156
Sucrose	29.4	118
Lard	18.3	165
Butter *	7.2	58
Salt mixture †	1.3	...
Bone ash	2.6	...
Total #	100.0	477

* Estimated as containing 90 per cent fat.
† Karr-Cowgill [17] salt mixture.
# One gram of this diet is therefore equivalent to 4.8 calories.

TABLE 2.—*Purified Casein Diet* *

	Per Cent	Calories
Casein† (87.1 per cent protein)	29.0	101
Sucrose	33.0	132
Lard	27.5	302
Butter fat	6.1	
Salt mixture ‡	1.6	
Bone ash	2.8	
Total §	100.0	535

* This ration was supplemented with 0.3 cc. of cod liver oil per kilogram per day, and with sources of antineuritic vitamin B.
† In this instance, casein refers to a highly purified product devoid of the water-soluble vitamin factors, obtained from the Harris Laboratories, Tuckahoe, N. Y.
‡ Karr-Cowgill [17] salt mixture.
§ One gram of this diet is therefore equivalent to 5.4 calories.

time no signs of vitamin B_2 deficiency, such as bloody diarrhea, cutaneous sores, buccal lesions and intense salivation (Goldberger and others [9]), were manifested.

Three of the eight animals (nos. 1, 5 and 6) on the deficient rations had a different nutritive history. These dogs had been used for another experiment, in which the ration employed was highly purified with respect to the heat-stable B_2 substance (table 2).

15. Evans, H. M., and Burr, G. O.: A New Differentiation Between the Antineuritic Vitamin B and the Purely Growth-Promoting Vitamin B, J. Biol. Chem. **77**:231, 1928.

16. Goldberger, J.; Wheeler, G. A.; Rogers, L. M., and Sebrell, W. H.: A Study of the Black Tongue Preventive Value of Leached Commercial Casein, Together with a Test of Black Tongue Preventive Action of a High Protein Diet, Pub. Health Rep. **45**:273, 1930.

The opportunity was presented to transfer two of these animals (nos. 5 and 6) to the casein III regimen, with a view to studying changes in the nervous system as affected by previous depletion of vitamin B_2. Dog 1 subsisted entirely on the highly purified casein diet. When symptoms of antineuritic vitamin B deficiency were manifested in these animals, a bloody diarrhea was observed in every case, indicative of a lack of the heat-stable factor.

Details of Feeding.—The dogs were given an allotment of food once a day in sufficient amount to maintain the body weight. Their intakes of food were determined daily, in order to see whether the severity of the pathologic process, as exemplified by damage to nerve tissue, could be correlated with the degree of anorexia characteristically exhibited by vitamin-B deficient animals.

Fasting Controls.—In addition, two animals (nos. 11 and 12) were entirely deprived of food, but given 1 Gm. of vitavose per kilogram per day as an adequate, exogenous source of the vitamin B complex. It was previously determined by Cowgill [17] that a daily intake of 0.6 Gm. of vitavose is sufficient to maintain perfect appetite in animals subsisting on the casein III diet. This dosage was raised to 1 Gm. in order to insure a reasonable factor of safety.

Normal Controls.—Two animals (nos. 9 and 10) were on diets complete in all respects and at no time displayed any manifestations of nervous disease.

Postmortem Examinations.—It was felt that destructive changes could be more readily detected if the pathologic process was made as severe as possible. The animals were therefore killed as near the point of death as could be judged, or were allowed to proceed to a fatal termination. Complete postmortem examinations were performed on the animals within four hours in every case. These included an examination of the sciatic nerves, the brachial plexuses, the median and ulnar nerves, the vagi and the whole brain and spinal cord with the nerve roots. In each instance, the paired nerves were examined for comparative purposes.

Histologic Technic.—Blocks of all organs (except the nervous system) found abnormal in the gross were fixed in Zenker's fluid to which acetic acid had been added and in a diluted solution of formaldehyde, U. S. P. (1:10), for staining with hematoxylin-eosin. The nervous system in each instance, both central and peripheral, was sectioned on removal from the body and fixed in 95 per cent alcohol, in a diluted solution of formaldehyde, U. S. P. (1:10), and in Müller's solution. The alcohol-fixed material was embedded in celloidin and stained by the original Nissl method (toluidine blue), with hematoxylin-eosin and by the Klarfeld tannic acid-silver carbonate method, when indicated. The formaldehyde-fixed material was employed in part for sudan III stains for fat, for the demonstration of axis cylinders by the Bielschowsky method and for the demonstration of myelin sheaths by the Spielmeyer method, and in part for the study of myelin sheaths by the Kulschitsky modification of the Weigert method. The material fixed in Müller's solution was stained with osmic acid, embedded rapidly in celloidin, and sectioned at 30 microns. In this way, it was hoped to obtain both a positive and a negative picture of any possible myelin degeneration.

EXPERIMENTAL RESULTS: CLINICAL FINDINGS

The length of the experimental period varied with the individual animal, but in dogs subsisting on casein III the symptoms usually

17. Cowgill, G. R.: An Improved Procedure for Metabolism Experiments, J. Biol. Chem. **56**:725, 1923.

appeared within from sixty to ninety days after the vitamin B complex was withheld.

The pathologic manifestations of vitamin B-deficiency as they occur in the dog have been described by Cowgill.[7] The first symptom is a dragging of the hind legs when the animal lifts itself upon its feet. These limbs remain extended when the dog walks, so that the typical reflex of extensor-flexor alternation is not exhibited. This maintained contracture of the hind limbs becomes more and more marked; the toes are curled in, so that the animal stands on its knuckles. Subsequently, a pronounced ataxia is manifested when the dog is allowed to walk.

The spastic paralysis progresses cephalad; eventually the fore limbs become involved, and finally the neck muscles. A marked opisthotonos is exhibited. The entire nervous system becomes hypersensitive, and tonic spasms are frequent.

In the advanced stages of the disease, severe, generalized convulsions are present. In some of the animals, the convulsions occur fairly soon

TABLE 3.—*Survival Period of Dogs on Vitamin B-Deficient Diets*

Dog	Survival Period, Days
1	1
2	7
3	5
4	1
5	3
6	2
7	1
8	3

and are the dominant part of the syndrome. These clonic spasms, which recur intermittently between periods of relaxation, are not unlike the picture produced by strychnine poisoning.

The period of survival after the appearance of the symptoms varied in this study between one and seven days, as table 3 indicates.

In general, it may be said that the survival period was shorter for those animals that manifested the convulsive seizures early. On the other hand, when the condition of progressive tonic spasticity was the first feature, the number of days the animals lived after the first appearance of the symptoms depended on how soon the clonic spasms occurred.

The syndrome exhibited by dog 4 was somewhat atypical. On the forty-fourth day, a convulsion occurred, involving the facial muscles. Frothing at the mouth and the nature of the convulsion suggested an epileptiform attack. On the fifty-first day, two such seizures occurred, and throughout the following morning they were exhibited in rapid succession between very short periods of relaxation, and resulted in the death of the animal early in the afternoon.

Dogs 1, 5 and 6 had been previously depleted of the heat-stable B_2 substance (see Experimental Procedure). They all vomited on the day preceding the neuritic manifestations. The foul breath and bloody diarrhea, which were accompanying features, suggested an alimentary disturbance, probably due to lack of vitamin B_2.

ANATOMIC FINDINGS

Findings other than those in the nervous system were but incidental to the purposes of this study and are recorded only in the individual protocols of these animals. On the basis of the histologic changes in the central nervous system, the eight dogs maintained on the vitamin

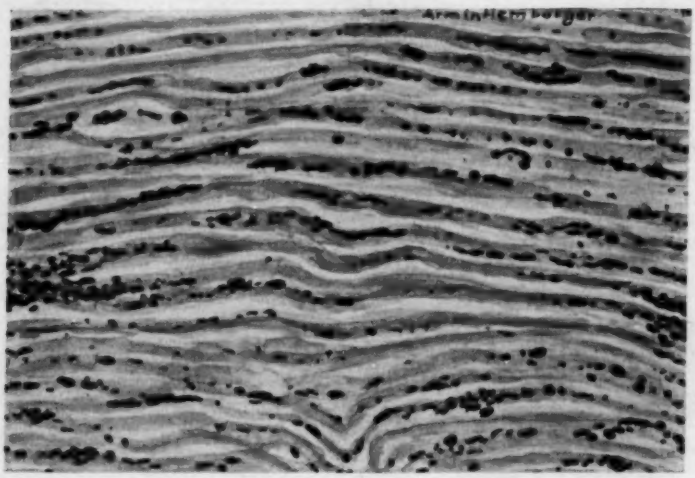

Fig. 1.—Drawing of a microscopic preparation of sciatic nerve of dog 6; Marchi; × 220.

B-deficient diets can be divided into two groups: group 1, comprised of dogs 1, 5 and 6, which were previously on a vitamin B_2-deficient diet, and group 2, comprised of dogs 2, 3, 4, 7 and 8, the ration of which lacked essentially the antineuritic factor.

Group 1.—On gross examination of dogs 1, 5 and 6, no abnormalities were noted in the covering of the brains and spinal cords. Multiple frontal sections of the cerebral hemispheres revealed no deviations from the normal in color and consistency. The brain stems and cerebella were similarly without change. Numerous transverse sections of the spinal cords at all levels revealed no anemia, hyperemia or softening. Likewise, all the peripheral nerves, including the vagi, were quite like those of normal animals.

In the Marchi preparations of the peripheral nerves, numerous clumps of black granules could be seen in most of their fibers (fig. 1). Often these dark bodies were concentrated at points where the fibers appeared to be swollen, and they lay within, and not outside of, the neurilemmas. In the same fiber they often appeared at several points, with granule-free zones intervening. The distal as well as the proximal portions of the nerves were equally involved, as were even portions of the brachial plexuses. In all three animals, the vagi showed the same myelin degeneration but to a less degree, and in general the median

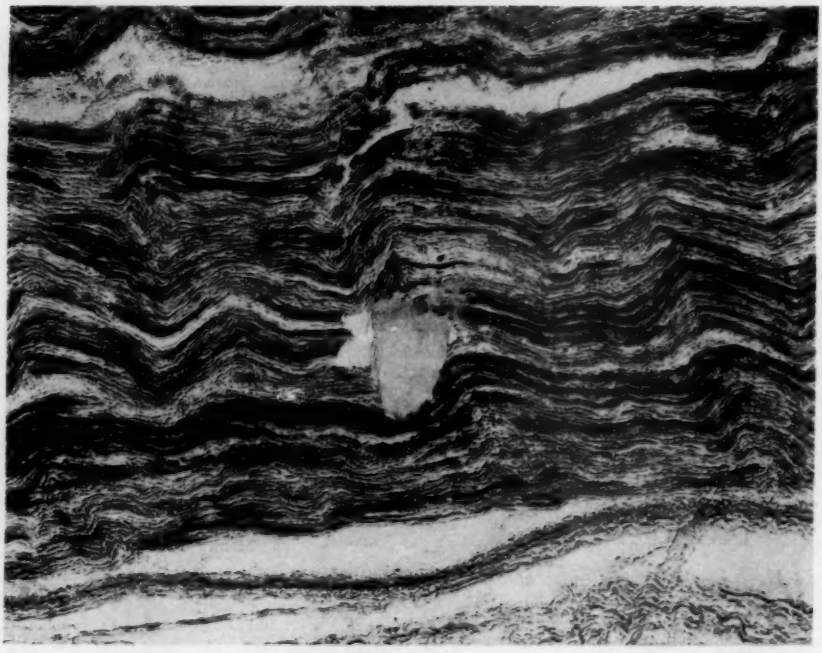

Fig. 2.—Photomicrograph of sciatic nerve of dog 6, showing extensive demyelination. A few fibers only show no degeneration along their whole course; Spielmeyer; × 60.

and ulnar nerves were somewhat less involved than the sciatic nerves. The most extensive changes of this character were present in dog 1, in which, also, the sciatic nerves showed more involvement than the other nerves examined.

Spielmeyer and Kulschitsky preparations of the same nerves showed comparable pictures of extensive demyelination (fig. 2). The widespread involvement noted in the Marchi preparations was confirmed by these stains. Again it could be noted that not invariably was the whole nerve fiber destroyed, but that along the course of a single fiber degen-

erated portions alternated with nearly normal portions. Some of the least involved fibers had a foamy appearance, but stained nearly as well as the completely normal fibers. Others showed swelling at irregular intervals, stained capriciously, and often contained round, gray granules of partially disintegrated myelin. Many of the individual nerve fibers failed to stain at all by either of these two methods.

In preparations stained with sudan III (fig. 3), the myelin sheath degeneration was again confirmed. In dogs 5 and 6, the peripheral nerves thus stained were seen to contain large and small clumps of granules of a brilliant orange-red color. Little or no fat was found lying between the nerve fibers; all seemed to be encased within the sheaths of Schwann. None of the fat was phagocytosed; indeed, no

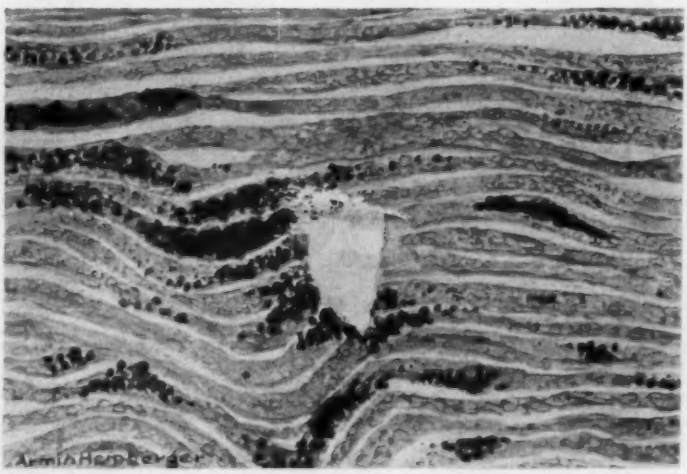

Fig. 3.—Drawing of sciatic nerve of dog 6; sudan III; × 220.

phagocytic cells were present in the nerves of these two animals. In dog 1, on the other hand, most of the brightly stained fat particles from the degenerated myelin sheaths in the sciatic nerves were phagocytosed in fat-granule cells, which were present in abundance (fig. 4). The vagi of dog 1 lacked fat-granule cells, although demyelination was fairly widespread and demonstrable with sudan III. Thus there is ample proof of an extensive degeneration of myelin in the vagus, sciatic, median and ulnar nerves and in the brachial plexuses of dogs 1, 5 and 6. This demyelination was present in the paired nerves to an approximately equal degree, but was most marked in the sciatics and least marked in the vagi. Moreover, in all the stains employed, the degenerative process displayed a striking parallelism as regards severity of involvement. It was impossible to determine whether the sensory

or motor components of the peripheral nerves were predominantly involved, but that both were involved was more than likely, as some nerves showed degeneration of nearly all the individual fibers.

There is no question but that the neurilemmas of the destroyed nerve fibers appeared more cellular, but there is some doubt that this was due to an actual proliferation of the cells of the sheaths of Schwann. It is conceivable that the atrophy of the nerve fibers following the disappearance of the myelin sheaths could produce a condensation of the Schwann cells to simulate an increase in their number. No cells undergoing mitotic division were demonstrable. Also, with an atrophy of many of the nerve fibers, the intervening connective tissue cells were brought into prominence. That many of these supposedly neurilemmal

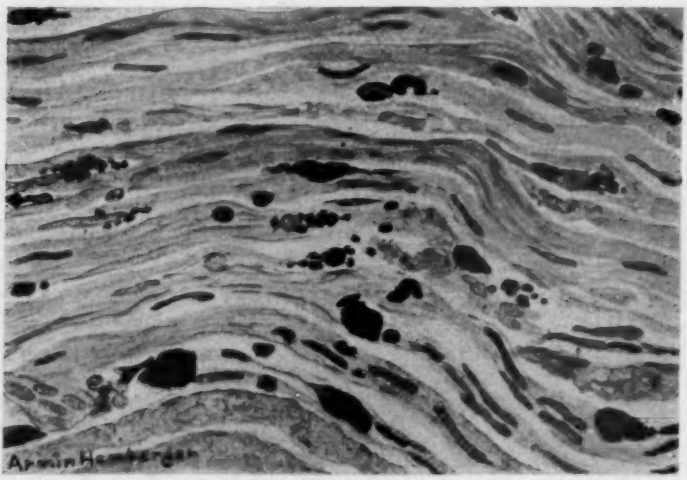

Fig. 4.—Drawing of sciatic nerve of dog 1, showing fat from degenerated medullary sheaths phagocytosed by fat-granule cells; sudan III; × 220.

cells had an elongated, oval shape like fibroblasts may not be without reason.

In contrast to the widespread and extensive demyelination of the peripheral nerves, the axis cylinders were intact almost without exception. That this was true for those nerves the myelin sheaths of which deviated but so slightly from the normal as to have a foamy appearance in the Spielmeyer stain or an occasional granule of fat in the sudan III stain is perhaps not surprising. But that the axis cylinders should be intact even in nerve fibers that had lost nearly all their myelin sheaths is a noteworthy finding. Only an occasional axis cylinder was fragmented or degenerated, and then only in the most severely demyelinated nerve fibers.

The spinal nerve roots, dorsal as well as ventral, showed no evidence of demyelination. The ganglion cells of the ventral and dorsal horns of the spinal cord in the Nissl preparations revealed well stained Nissl bodies. The nuclei had prominent, well stained nucleoli, and lay in central positions within the cells. There was no pigmentation of the cellular cytoplasm and no chromatolysis. The whole length of Goll's column in dog 1 was replaced by a marked glial reaction in which were present fibrillary astrocytes, rod-shaped Hortega cells and myeloclasts, the latter in predominant numbers (fig. 5). Fat-granule cells were

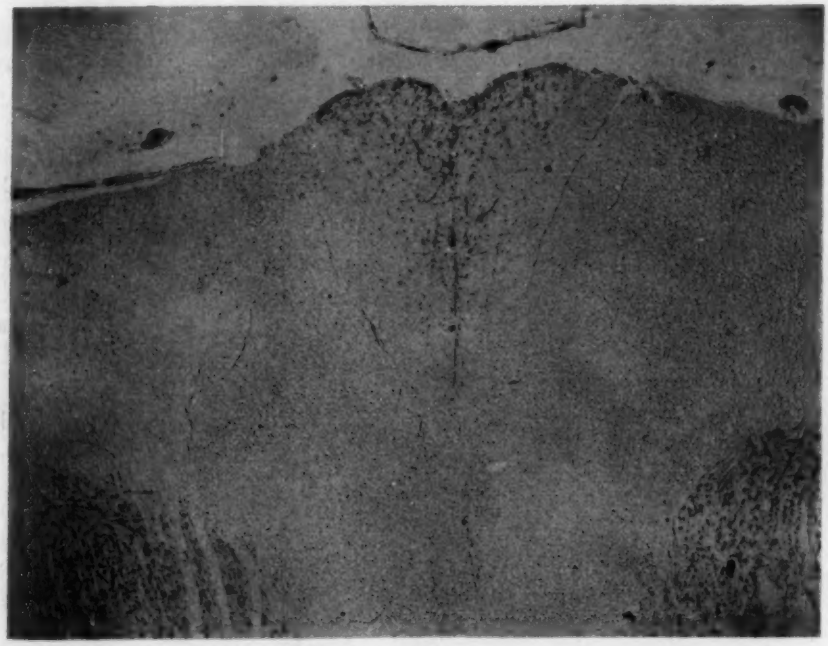

Fig. 5.—Photomicrograph of dorsal columns in the spinal cord of dog 1. Note the triangle-shaped glial reaction in the median dorsal fasciculi; Nissl; × 45.

absent. This glial response had a wedge-shaped outline with the base toward the pial surface, and lay in a symmetrical position on each side of the posterior median septum. In neither of the other two dogs was any such reaction present in the white matter of the spinal cord.

The Kulschitsky preparations were entirely negative for evidences of degeneration in dogs 5 and 6, and in areas other than the fasciculus gracilis in dog 1. In this fasciculus, the myelin destruction was unquestionable, and corresponded identically with the shape and position of the glial reaction noted in the Nissl stains (fig. 6). It was sur-

prising, therefore, in view of the otherwise negative findings in the Kulschitsky stains, to find in the Spielmeyer preparations of all three animals that there were numerous large, irregular, patchy, unstained areas that superficially resembled demyelination (fig. 7). Their patchy distribution was that of a combined system disease, but the myelin sheaths in them did not have the appearance of destruction. Rather, these sheaths seemed simply to have failed to stain, but were visible as apparently intact structures under high magnification. This point was settled in the Marchi preparations of the spinal cord, where no degen-

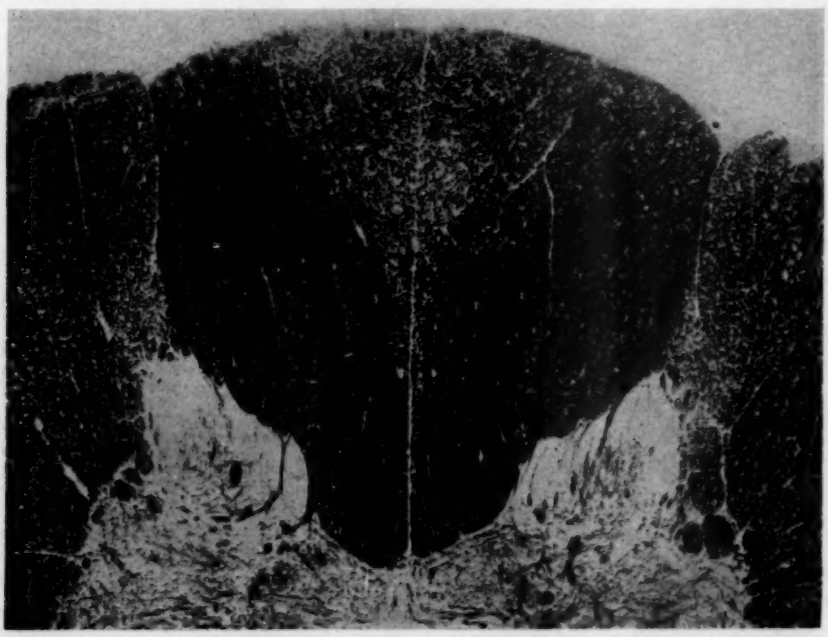

Fig. 6.—Photomicrograph of spinal cord of dog 1, showing demyelination in the median dorsal fasciculi; Kulschitsky; × 40.

erated sheaths were found except in the medial dorsal columns of dog 1. To be sure, an isolated black granule was found here and there in other parts of the white matter, but it invariably lay outside of a sheath and was of an extraneous source. Similarly devoid of evidence of myelin destruction in the spinal cords were the sudan III stains, which failed to demonstrate fat even within the medial dorsal columns. Another point that needs mention is the fact that preparations in serial section of blocks of spinal cord stained by the Spielmeyer method never showed the unstained areas in precisely the same place in two consecutive preparations. These facts prove that there was no genuine com-

bined system disease in these animals, as the Spielmeyer preparations would appear to indicate.

The cortical cyto-architecture of the cerebral hemispheres as seen by the toluidine blue stain was completely normal. The vast majority of cortical nerve cells were stained well, had centrally placed nuclei, and contained the usual Nissl apparatus. Only a rare ganglion cell showed acute swelling with vacuoles in its cytoplasm. A particularly normal picture was presented by the large cells of Betz. No abnormalities were found in any of the nerve cells of the basal ganglions. The first

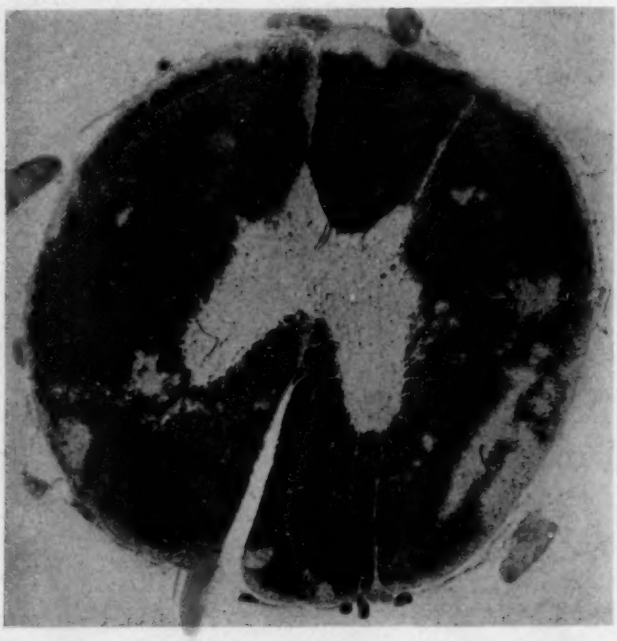

Fig. 7.—Photomicrograph of spinal cord of dog 6, stained by the Spielmeyer method. Note numerous patchy unstained zones (cf. fig. 13) similar to those observed in "combined system disease"; × 16.

deviation from the usual picture was encountered in all three animals in the region of the substantia gelatinosa rolandi (fig. 8). This bilateral lesion consisted of an extensive destruction of these zones with a marked vascular as well as glial proliferation. Many vessels of capillary size had large, swollen endothelial cells, the nuclei of some of which were in some stage of mitotic division. That these small vessels were greatly increased in number was excellently demonstrated in the Klarfeld preparations. The glial cells were of several types, with various forms of Hortega cells and oligodendroglia predominating. Many of

the transformed microglia were present as large, round mononuclear cells containing phagocytosed débris in their cytoplasm. Immensely swollen oligodendroglia cells were found in large numbers; these were often several times greater in size than the phagocytic microglia. They had small, eccentrically placed nuclei and an abundance of cytoplasm, which had a diaphanous, foamy appearance (fig. 9).

The whole cerebellum was devoid of changes, except for the vermis. This structure in all three animals was involved in an equal manner and to an equal degree. The mode of involvement was identical with

Fig. 8 (dog 5).—Photomicrograph of cellular and myelin destruction and glial and vascular proliferation in region of substantia gelatinosa rolandi; Nissl; × 60.

that in the substantia gelatinosa—there were regressive glial and vascular proliferation (fig. 10). In the implicated part, the Purkinje cells were completely destroyed, and the granular cells were decreased in number, presenting a moth-eaten appearance. Except for the vermis and for the regions of the substantia gelantinosa of the pons and medulla, all the fat and myelin sheath stains of the cerebra, ponti, cerebella and medullae were negative.

Group 2.—As was the case in the animals of group 1, no changes were found grossly in the nervous systems of the animals in group 2.

Microscopically, however, lesions were also encountered in these animals. The peripheral nerves showed myelin destruction that compared closely with that found in group 1. In addition, however, the interesting fact came to light that there was a definite parallelism between the length of time the clinical symptoms of paralysis persisted and the extent of the anatomic lesion in the nerves. Dog 2 (symptoms for seven days), for example, showed more marked destruction of the sciatic nerves than any other animal in the series. Its median, ulnar and vagus nerves were more extensively destroyed than were the same

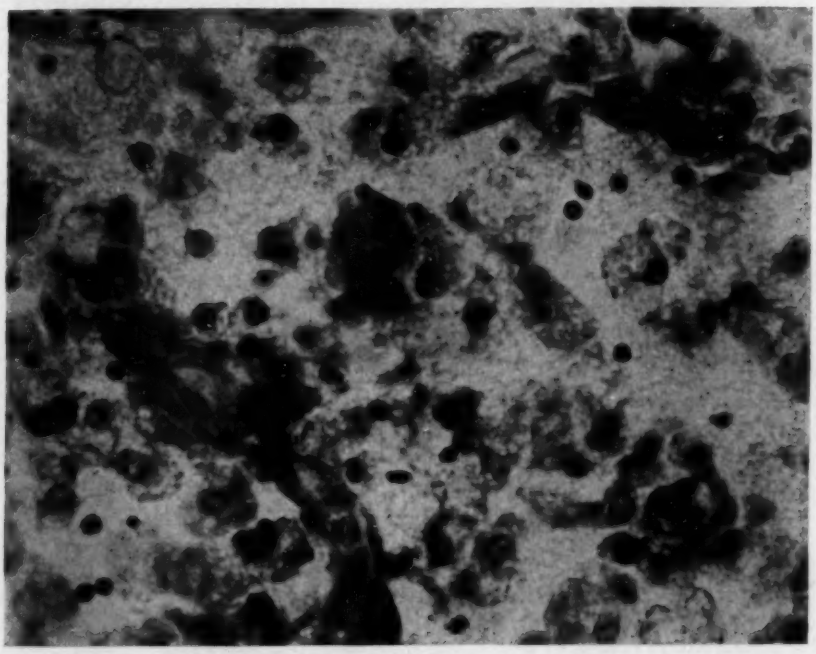

Fig. 9 (dog 5).—Photomicrograph of fat-granule cells and swollen oligodendroglia in region of substantia gelatinosa rolandi; Nissl; × 550.

nerves in other animals. Again, the demyelination in dog 3 (symptoms for five days) was more extensive than in animals 4 and 7, which had symptoms for but a single day. That the parallelism between the severity of the anatomic lesion and the duration of symptoms was not entirely complete was demonstrated by dog 1 (symptoms for one day), the peripheral nerve lesions of which almost approached in severity those of dog 2. However, dog 1 had subsisted throughout the entire experimental period on the more highly purified casein ration (table 2), and for this reason it is unfair to compare the lesions of this animal with those in group 2.

There was no uniform change in the ganglion cells of the ventral and dorsal horns of the spinal cords. Indeed, the majority of these cells presented the modal picture. An occasional cell, in the midst of a group of normal ones, was unusually deeply stained, and its Nissl bodies were obscured. Very few cells showed acute swelling. The impression was gained that in spite of these minor changes in the ganglion cells no definite deviation from the normal was present in the anterior and posterior horns. In dog 4, an occasional ganglion cell

Fig. 10 (dog 5).—Photomicrograph of the degenerative process in the vermis cerebelli, showing loss of Purkinje cells and marked alteration of the granular cell layer. Note the increase in the number of blood vessels; Nissl; × 45.

in the anterior motor horn was deeply stained, its cellular contents were hardly recognizable, and it had a few pericellular incrustations.

The Marchi, Kulschitsky and sudan III stains were all negative for myelin destruction in the spinal nerve roots as well as in the spinal cords themselves. The Spielmeyer method alone yielded results of the type described for group 1 and illustrated in figure 7. All these stains when applied to the cerebrum, cerebellum and brain stem yielded negative results.

The cerebral cortical cellular architecture was intact in all the animals of this group, except in dog 4. In this animal, which had epileptiform convulsions, numerous zones were found in the cerebral cortex where there was a partial or complete loss of the cortical laminae. One such area is shown in figure 11, where the paleness of the gyrus in the paracentral lobule was produced by a diffuse destruction of ganglion

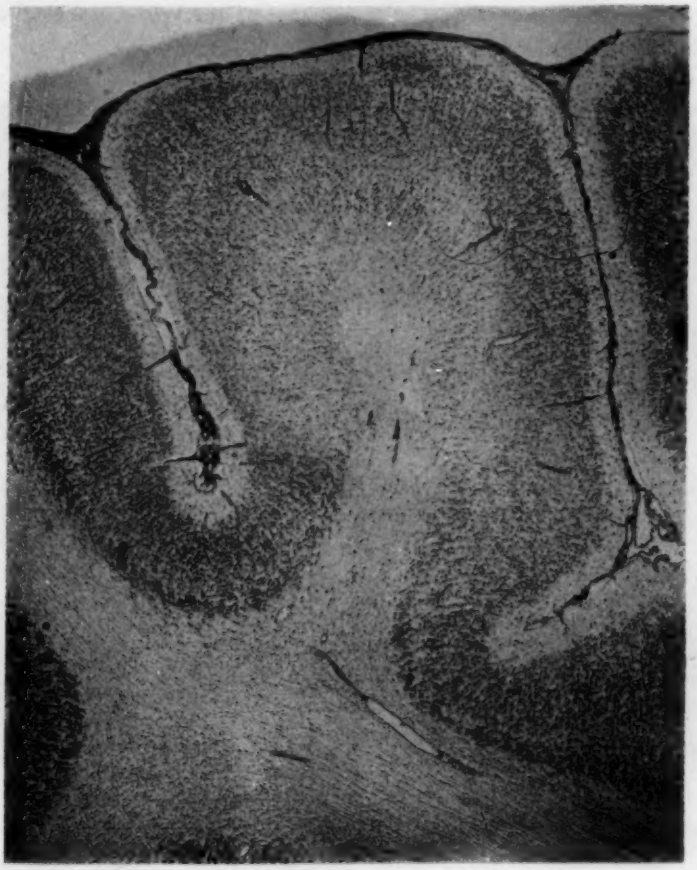

Fig. 11 (dog 4).—Photomicrograph of cerebral cortex showing diffuse loss of ganglion cells in the crest of a gyrus; Nissl; × 18.

cells of an ischemic type. These ischemic changes, unaccompanied by any demonstrable organic vascular lesions, were widespread. The cornu ammonis formation was no more extensively involved than were some lobules in the frontal, parietal and occipital lobes.

Fasting Controls.—In both animals of the fasting group, no changes were found on gross examination of the nervous system. Microscopi-

cally, however, the peripheral nerves showed a moderate degree of demyelination in the myelin sheath stains. In confirmation of this, the Marchi method applied to the nerves revealed a considerable number of black granules in dog 12 (fig. 12) and a small number in dog 11. But in the sudan III preparations only a very small amount of stainable fat was demonstrable.

The spinal nerve roots failed to show myelin destruction by any of the methods employed. Cross-sections of the spinal cords, however, revealed an occasional black ringlet by the Marchi method, representing

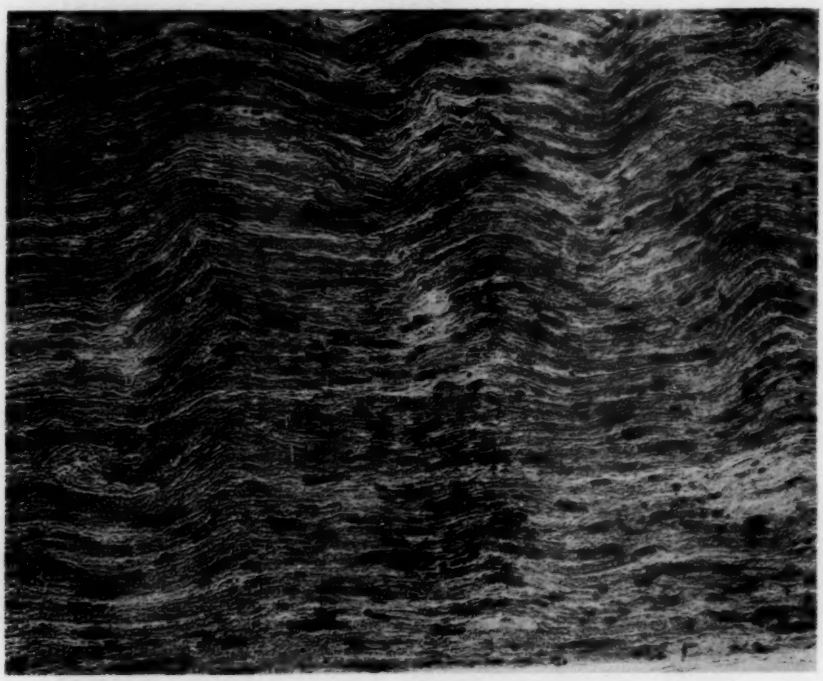

Fig. 12.—Photomicrograph of sciatic nerve of dog 12, showing numerous black granules of myelin degeneration by the Marchi method; × 125.

a degenerated sheath. There was no uniformity nor apparent seat of predilection to the occurrence of these ringlets, for they sometimes were present in a sensory and sometimes in a motor column. The sudan stains were essentially negative and the Kulschitsky stains completely so. In the Spielmeyer preparations of these cords were present the same unstained patches noted in all the cords thus far described.

Ganglion cell changes in the ventral horns of the cord of a type seen in the animals of the two preceding groups, namely, loss of distinctness of cytoplasmic detail and deep staining, were present to a

slight degree in the animals of this group as well. No changes, however, were present in the nerve cells elsewhere than in the spinal cords. Each cerebral hemisphere, cerebellum, pons and medulla was completely normal as regards the cellular constituents, the myelin sheaths and the axis cylinders.

Normal Controls.—The peripheral nerves were completely negative as far as evidences of a genuine demyelination were concerned. In the Marchi preparations only was an occasional black granule seen within a neurilemma. Finding such solitary granules of degenerated myelin

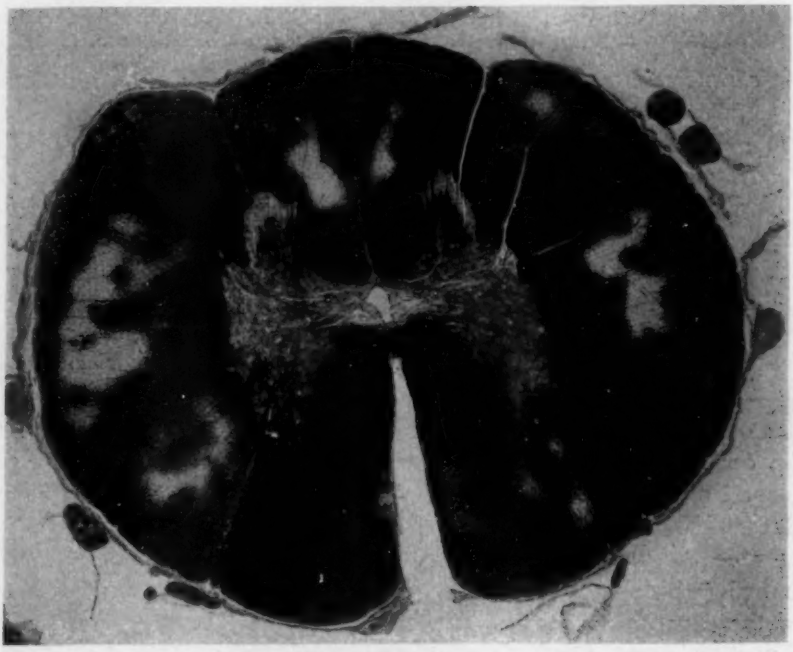

Fig. 13.—Photomicrograph of spinal cord of dog 10 stained by the Spielmeyer method. Note the unstained zones (cf. fig. 7); × 15.

in what were quite obviously normal nerves would indicate that they were without pathologic significance. An occasional degenerated myelin sheath was also found in the preparations of the spinal cord treated with osmic acid, and was likewise, quite probably, without significance. The Kulschitsky stains and the sudan III stains of the spinal cords were completely negative, but in the Spielmeyer preparations patchy, unstained zones were present rather conspicuously (fig. 13). And these in the cords of normal control animals that at no time displayed neurologic manifestations!

An occasional anterior horn motor cell was deeply stained and lacked a well defined Nissl apparatus. From this it must be concluded that findings of a similar nature in all the animals previously described were of minimal, if any, significance. No lesions of any kind were demonstrable in the cerebral hemispheres, the brain stem and the cerebellum by any of the histologic methods employed.

Summary of Anatomic Findings.—In none of the twelve animals studied was there any gross evidence of disease in the central and peripheral nervous systems. Microscopically, a peripheral polyneuritis, in the sense of myelin degeneration, was found in the sciatic, median and ulnar nerves, the brachial plexuses and the vagus nerves, decreasing in severity in the order named, and involving all the animals except the two normal controls (dogs 9 and 10). The neuritis implicated the bilateral nerves to an equal degree, was as marked in the proximal as in the distal portions of each nerve, and appeared to parallel in severity the duration of the clinical symptoms, except in the starvation controls (dogs 11 and 12), which did not develop paralytic manifestations. In the latter two animals the neuritis, though definitely present, was decidedly less marked than in the animals maintained on a vitamin B-deficient ration. The involvement of the axis cylinders was trivial, even in those nerves in which the myelin destruction was severe.

In none of the animals were changes found in the spinal nerve roots. Tigrolysis, pigmentation and acute swelling were present in an occasional anterior horn motor cell in the spinal cords of all the animals. An occasional black ringlet of myelin degeneration was found by the Marchi method in the experimental animals, as well as in the controls. Sudan III preparations of the spinal cord were invariably negative, as were the modified Weigert preparations except in dog 1. In this animal (which was on a highly purified diet during the whole course of the experiment), there was degeneration of the fasciculus gracilis demonstrable not only in the Kulschitsky preparations, but in the Marchi and Nissl preparations as well. In the latter stains, it was seen that the median dorsal fasciculi contained numerous regressive glia—microglia and myeloclasts.

In the Spielmeyer preparations of all the spinal cords, of the normal controls, the fasting controls and the animals on vitamin B-deficient diet, there were found disseminated, large, irregular, unstained areas involving motor as well as sensory tracts. In serial sections stained by this method, it was noted that the unstained patches in no two consecutive preparations occurred in precisely the same location.

In dogs 1, 5 and 6, which were either entirely or partially on the purified casein diet (table 2), there were found large zones of degeneration and vascular proliferation in the vermis of the cerebellum and

the regions of the substantia gelatinosa rolandi of the pons and medulla. These lesions were present only in the three dogs enumerated and were strikingly similar as regards the type, the location and the bilateralism (substantia gelantinosa) of the involvement.

The remainder of the central nervous system revealed no pathologic changes by any of the methods of study employed in these experiments, excepting dog 4. In the cerebral cortex of the latter animal, which had unusual epileptiform seizures in addition to the more usual paralytic symptoms, there were found disseminated ischemic necrobiotic foci in the Nissl preparations. These lesions were not associated with any demonstrable organic vascular changes.

COMMENT

From these studies on the dog the anatomic findings resulting from lack of the antineuritic factor in pigeons and rats have been confirmed as far as concerns a noninflammatory peripheral polyneuritis. Further, the fact is substantiated that even with very severe lesions of the medullary sheaths the axis cylinders of the peripheral nerves suffer a minimal degree of damage. A finding of decided interest, however, is the polyneuritis observed in the dogs (nos. 11 and 12) that were totally deprived of food except for the calculated daily requirement of the vitamin B complex. Mention has been made in an earlier part of this paper of similar observations by Woollard [8] on the rat, but he noted, as did we in the dog, that in these animals the myelin destruction was not as marked as in those that received a vitamin B-deficient diet. Neither the dogs nor the rats at any time displayed signs of a neuromuscular lesion clinically, and therefore, on first thought, it would appear that a polyneuritis could not be held responsible for the neurologic syndrome observed in the vitamin B-deficient animals. Only it must be noted that death occurs much sooner in the completely starved dogs (fifteen and thirty-five days, respectively, in the two animals of this study) than in those maintained on a vitamin B-deficient ration. Is it not possible that inanition in itself is capable of producing the observed polyneuritis, but that early death interferes with the onset of the clinical symptoms of paralysis and ataxia? The less severe anatomic lesion in the peripheral nerves of the starved controls, as contrasted with that in the vitamin B-deficient animals, would tend to substantiate this hypothesis.

To attempt to explain all the neurologic signs on the basis of a polyneuritis is unwarranted, particularly the convulsions and opisthotonos. A great variety of lesions—in the anterior horn motor cells of the spinal cord, in the medullary sheaths of the spinal cord and cerebrum and even in the cerebral cortical ganglion cells—are held

responsible for these clinical signs by a variety of workers. Lesions of such nature, namely, chromatolysis, pigmentation and shrinkage of the anterior horn motor cells and degeneration of an occasional myelin sheath in the spinal cord, have been observed in this study, but never to a degree greater than in the normal control animals. It would appear, therefore, that they play no rôle in the pathogenesis of these nervous symptoms.

In this connection, the findings in dog 4 are of especial interest. This animal had epileptiform seizures with foaming at the mouth and marked retractions of the head. At necropsy, the cerebral findings were identical in many respects with those reported by Spielmeyer [18] and by DeVries [19] as the result of functional vascular spasms. Cortical necrobiotic foci occur, particularly in the cornu ammonis formation, in certain forms of epilepsy, and in other parts of the cerebral cortex in such diverse conditions as manic depressive psychosis, carbon monoxide poisoning, eclampsia and uremia. In many such instances, no organic vascular lesions are demonstrable, and it is held that ischemia on a functional basis is the underlying cause of these anatomic alterations. Not all cases of epilepsy, however, show necrobiosis, and it is believed that fairly prolonged and repeated attacks of functional vascular occlusion are necessary before these changes take place. It is at least of interest to speculate whether some of the manifestations observed in B-avitaminosis are not due to just such causes, namely, functional vascular disturbances in the central nervous system.

The work of Gildea, Kattwinkel and Castle [12] already referred to, on a combined system disease in the spinal cord, portrays lesions by the Spielmeyer technic identical with those described in this study. From the facts that these large patchy unstained zones in the cord were demonstrable only by the Spielmeyer method, that they failed to occur in the same location in any two consecutive preparations, and that they were found in the normal controls as well as in the fasting controls and vitamin B-deficient animals, it must be concluded that they represented merely artefacts produced by the staining technic. Artefacts of this nature are not infrequently encountered in this method even in human material when the various steps in staining are not scrupulously adhered to, particularly as regards washing in 70 per cent alcohol following the "iron alum mordant."

It is to be noted that the three animals subjected completely or in part to deprivation of the pellagra-preventive factor (B_2) displayed a multiplicity of anatomic changes in addition to the peripheral poly-

18. Spielmeyer, W.: Kreislaufstörungen und Psychosen, Ztschr. f. d. ges. Neurol. u. Psychiat. **123**:536, 1930.

19. DeVries, E.: Acute Diseases of the Brain Due to Functional Disturbance of the Circulation, Arch. Neurol. & Psychiat. **25**:227, 1931.

neuritis. One such change was the demyelination of the median dorsal columns in dog 1, a finding similar to that described by Winkelman [20] in one of four cases of human pellagra. In a study of seven cases of human pellagra with nervous manifestations, Pentschew [21] found sclerotic changes in the spinal cords in four instances. These lesions, however, were not solely confined to the dorsal columns and this worker concluded that the neurologic changes in pellagra cannot be characterized as a "system disease."

Pentschew described in the first case of his series an atrophy and sclerosis of one of the cerebellar lobules, and in the fourth case an "inflammatory and degenerative" lesion in the locus caeruleus of the pons. In this connection, it is interesting to bear in mind the lesions of all three animals that were deficient in the B_2 factor. Whether the findings observed in Pentschew's cases and those in our three animals are, however, more than coincidental must remain a mooted question.

Pappenheimer and Goettsch [22] recently described softenings in the cerebellum in chicks, which they attributed to a lack of vitamin E. They do state, however, that their diets may not have been adequate as regards the water-soluble B vitamins. It is interesting that these lesions in the cerebellum in chicks are in every way identical with the cerebellar lesions present in the vitamin B_2 deficient dogs of our study.

CONCLUSIONS

Extensive demyelination was present in the sciatic, median, ulnar and vagus nerves and in the brachial plexuses of dogs deprived of the water-soluble B vitamins.

This myelin destruction was most severe in the sciatic and least severe in the vagus nerves of all the animals subsisting on a vitamin B-deficient ration.

The extent of the anatomic alterations in the peripheral nerves varied in direct proportion to the severity and duration of the paralytic symptoms.

Peripheral polyneuritis of the same type, but of a less degree, was present in the control animals, which were entirely deprived of food but supplied with an adequate amount of the B complex.

Ganglion cell changes and disseminated foci of myelin destruction in the brain or spinal cord could not be held responsible for the clinical symptoms of this nutritional disorder.

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20. Winkelman, N. W.: Beiträge zur Neurohistopathologie der Pellagra, Ztschr. f. d. ges. Neurol. u. Psychiat. **102**:38, 1926.

21. Pentschew, A.: Ueber die Histopathologie des Zentralnervensystems bei der Psychosis pellagrosa, Ztschr. f. d. ges. Neurol. u. Psychiat. **118**:17, 1928.

22. Pappenheimer, A. M., and Goettsch, M.: A Cerebellar Disorder in Chicks, Apparently of Nutritional Origin, J. Exper. Med. **53**:11, 1931.

Dogs deprived wholly or in part of the thermostable B_2 factor showed large zones of degeneration and vascular proliferation in the vermis of the cerebellum and in the region of the substantia gelatinosa rolandi.

The dog that had subsisted throughout the entire experimental period on the highly purified ration deficient only in the heat-stable factor (B_2) evidenced degeneration in the fasciculus gracilis of the spinal cord.

PROTOCOLS

Dog 1.—A female, weighing 9 Kg., subsisted on the highly purified casein diet supplemented with subminimal amounts of antineuritic vitamin B (table 2). The first appearance of symptoms occurred on the fifty-seventh day. The syndrome was exhibited in its most acute aspects. Both hind and fore limbs were severely paralyzed; convulsions were frequent, with marked opisthotonos. The body temperature was 101 F. Bloody diarrhea was present. The animal died within sixteen hours after the onset of the symptoms. Its final weight was 6.8 Kg.

Examination was performed one hour post mortem. The positive observations included dilatation of all four cavities of the heart, somewhat enlarged adrenals, several erosions of the mucous membrane in the ileum and larger ulcerations in the rectum. The buccal and gingival mucous membranes were unaltered.

Dog 2.—A male, with an initial weight of 10.6 Kg., subsisted on casein III. After a three weeks' period of perfect appetite, the intake of food became erratic until the fortieth day, after which anorexia was broken by only a few intermittent days of partial ingestion of food. The first signs of antineuritic vitamin deficiency were manifested on the sixty-eighth day. Until the seventy-fourth day, characteristic convulsions occurred with progressively greater frequency. The animal was killed the following morning. Its final weight was 7.5 Kg.

Examination was made three hours post mortem. The entire body, except the nervous system, was without abnormalities.

Dog 3.—A male, weighing 10.6 Kg., subsisted on casein III. The animal ate fairly well throughout the period, although the intake of food was erratic in the latter half of the experiment. On the seventy-first day, a maintained contracture of the hind legs was observed. By the seventy-fourth day, the dog exhibited a pronounced ataxia when allowed to walk around the room. During the afternoon of the same day, the animal became hypersensitive to tactile stimulation, with the consequent occurrence of tonic and clonic spasms, marked opisthotonos being present. The convulsions occurred more and more frequently until, on the seventy-fifth day, the animal was killed with a lethal dose of iso-amyl-ethyl barbituric acid. Its final weight was 9.6 Kg.

Examination was made one hour and fifteen minutes post mortem. The positive findings included a large subepicardial hemorrhage over the anterior surface of the left ventricle. A section of the myocardium revealed fibrosis and a recent hemorrhage in the musculature of the left ventricle. The adrenals and the pancreas were of normal size and texture. The intestinal mucosa was pale and intact.

Dog 4.—A female, with an initial weight of 18.3 Kg., subsisted on casein III. After two weeks of perfect intake of food, complete anorexia persisted until the end of the experimental period. On the forty-fourth day, an epileptiform convulsion occurred, after which the animal did not exhibit any more signs of antineuritic vitamin deficiency until the fifty-first day. On this day, three such convulsions were observed, involving the facial muscles as well as the body

musculature. The animal frothed at the mouth during the spasms. Throughout the subsequent morning, severe, generalized convulsions occurred in rapid succession. The dog died at 3:30 p. m. on the fifty-second day. Its final weight was 12.4 Kg.

Necropsy was performed three hours post mortem. There were hypertrophy and dilatation of the right cardiac ventricle. The adrenals were normal in size, color and consistency. There were worms in the small intestine, but there was no ulceration of the mucosa. The gums were normal.

Dog 5.—A male, weighing 6.5 Kg., had subsisted on the highly purified casein diet supplemented with antineuritic vitamin B, but deficient in vitamin B_2. After receiving a large dose of whole yeast, the animal was transferred to casein III, the antineuritic substance (B_1) being withheld. After a week of perfect appetite, the intake of food became erratic until the twenty-seventh day, following which complete anorexia ensued. The animal vomited on the fortieth day. On the forty-first day, spasticity of the hind legs was apparent. By the forty-second day, the dog could not rise to its feet, and on the subsequent day it remained in an opisthotonic position, with maintained extension of all limbs. A bloody diarrhea was present. The animal died at 12 noon. Its final weight was 4.9 Kg.

Necropsy was performed one hour post mortem. The heart was flaccid and dilated. There was focal pneumonia in the right lung on gross and microscopic examination. The adrenals were normal. Numerous hemorrhages and marked congestion were seen in the intestinal mucosa, but no ulceration. There were hair balls in the stomach and colon. The gingivae were normal.

Dog 6.—A male, with an initial weight of 5.9 Kg., had subsisted on the purified casein diet supplemented with vitamin B_1, but deficient in the B_2 substance. It was given a large dose of whole yeast and transferred to casein III. On the forty-third day, the animal vomited and exhibited a marked incoordination of gait. Bloody diarrhea was observed. The dog died on the forty-fourth day with typical symptoms. Its final weight was 8.4 Kg.

Examination was made thirty minutes post mortem. The heart was normal. There was focal pneumonia in the right lung. The duodenal mucosa had several eroded zones about 1 cm. in greatest diameter from which there was bleeding into the duodenal lumen. There were numerous superficial ulcers, the size and shape of solitary lymph follicles and Peyer's patches, in the large and small intestine. There was frank hemorrhage in the ileum. The adrenals were grossly and microscopically normal. There were no changes in the gums.

Dog 7.—A male, weighing 9.9 Kg., subsisted on casein III. After sixteen days of perfect appetite, the intake of food was erratic until death. On the thirty-seventh day, an acute onset of the symptoms characteristic of antineuritic vitamin deficiency occurred. Spastic paralysis of the limbs progressed cephalad very rapidly, and convulsions recurred frequently. Marked opisthotonos was observed. The animal died at 9 p. m. the same day. Its final weight was 8.4 Kg.

Examination was made two hours post mortem. All four ventricles of the heart were dilated, but without cardiac hypertrophy. Worms were present in the ileum, as well as an occasional small mucosal erosion. No abnormalities were noted in the adrenals or in the gums.

Dog 8.—An old female, weighing 12.4 Kg., after ninety days of subsistence on the casein III ration, was observed to eat its feces; in this way, it was securing some of the missing essential daily and thereby delaying the development of symptoms. The animal was muzzled. On the one hundred and sixth day, the symptoms of vitamin B_1 deficiency were manifested as a persistent extension of the hind

legs and an incoordination of gait. The symptoms became more severe during the three subsequent days, convulsions occurring very frequently on the one hundred and eighth day. The animal died the following morning. Its final weight was 10 Kg.

Necropsy was performed four hours post mortem. Flame-shaped hemorrhages were seen in ventricular endocardium and in the myocardium. There were no ulcers in the intestines; there were no lesions in the adrenals or in the gums.

Dog 9.—A large normal male subsisted on a ration employed for stock animals and found adequate in all essentials as far as known. At no time did it present nervous manifestations.

It was killed and examined immediately. The results were negative.

Dog 10.—A large male with a Pavlov pouch used for studies on gastric secretion was killed with iso-amyl-ethyl barbituric acid and examined immediately. The results of the entire postmortem examination were negative.

Dog 11.—From a male, weighing 5 Kg., food was completely withheld except 1 Gm. of vitavose per kilogram per day to supply a sufficient amount of the B complex. Water ad libitum was allowed. The animal died fifteen days from the beginning of the fast. No paralytic symptoms were observed.

Necropsy was performed two hours and forty-five minutes post mortem. There were no positive findings except marked emaciation and changes in the nervous system.

Dog 12.—A female, weighing 6 Kg., was starved completely except for 1 Gm. of vitavose per kilogram per day. The intake of water was not restricted. The animal died thirty-five days from the beginning of its fast.

Necropsy was performed four hours post mortem. The results were completely negative except for marked emaciation and changes in the nervous system.

RENAL DENERVATION

THE EFFECT OF SNAKE VENOM AND CHILLING ON THE RENAL VASCULARIZATION *

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In the case history of the nephritic patient one clinical observation has been established as common—the "chill," or at least the exposure to cold. Of course, we may not find it in the history of each patient, but it occurs with such frequency that etiologic significance has always been attached to it.

It is known that following chilling the urine of presumably normal persons may occasionally contain albumin, some red blood cells and casts; in persons with vasomotor lability, this occurs rather frequently.

The fact that under normal conditions the vascular bed of the kidney receives a proportionally large share of the total circulating blood is also well established, as is the fact that ischemia is followed by obvious functional and histologic evidence of renal degeneration, if the condition obtains for any length of time (thirty minutes or more).

In previous papers,[1] we have shown the intimate autonomic coordination that exists between the vascular bed of the skin and the internal organs; when chilling occurs, the vascular bed of the splanchnic area dilates (stomach, intestines, liver, pancreas and spleen), but the renal vessels apparently contract synchronously with the skin.

We have repeatedly called attention to the significance of the state of the vascular bed of an organ in relation to resistance against injury and infection,[2] a factor that is of particular importance in organs with great metabolic demands (such as the kidney) where vascular spasm may become a factor of paramount interest.

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1. Petersen, W. F., and Müller, E. F.: The Splanchno-Peripheral Balance, Arch. Int. Med. **40**:575, 1927.

2. Müller, E. F., and Petersen, W. F.: Ueber den Infectionsschutz des Lebergewebes bei experimenteller Sepsis, Ztschr. f. exper. Path. u. Therap. **66**: 442, 1929.

As a matter of fact, the significance of arteriolar spasm in the pathogenesis of renal disease has been repeatedly suggested, particularly in the arteriosclerotic types of nephritis.

Some years ago, when studying the effects of prolonged continuous intravenous injections of Bacillus coli (whereby the typical picture of a sepsis could be obtained), we observed [3] the rapid appearance of albumin, red blood cells and casts in the urine in association with the onset of the chill in the animal. We then proceeded to a study of such urinary changes when the kidney had been denervated.

In these experiments, we found that when B. coli was injected intravenously over long periods of time, the urine from the denervated kidney remained free from albumin, red blood cells or casts, while the urine from the normal kidney contained them from the time of the first chill.[4] The urine from the denervated kidney remained free from the bacteria and that from the normal kidney contained them in large numbers.

A latent period of approximately half an hour usually followed the injection of the bacteria into dogs before the onset of a chill. We therefore proceeded next to chill the animals artificially and simultaneously with the beginning of the injection. It was then found that the urine from the denervated kidney remained normal, while the urine from the normal kidney contained red blood cells, casts, albumin and bacteria from the very beginning of the injection.[5]

From these considerations and observations we felt justified in implicating both the vasomotor status and the varying toxic agent in the production of the nephritic picture.

RENAL INNERVATION

The innervation of the kidney was reviewed by Kuntz,[6] who concluded that the nerves are vasomotor and chiefly vasoconstrictor. Kaufmann and Gottlieb [7] demonstrated nerve fibers to the tubules, to

3. Petersen, W. F.; Milles, G., and Müller, E. F.: Ueber Aenderungen des Kalium—Calcium Quotienten der Lymphe bei experimenteller Sepsis, Ztschr. f. exper. Path. u. Therap. **60**:336, 1928.

4. Müller, E. F.; Petersen, W. F., and Rieder, W.: Die Bedeutung des vegetativen Systems für die Entstehung der primären Nierenschädigungen im Anschluss an Erkältungen und Infektionen, Verhandl. d. deutsch. Gesellsch. f. inn. Med. **42**:580, 1930.

5. Footnote 5 deleted by the author.

6. Kuntz, A.: The Autonomic Nervous System, Philadelphia, Lea & Febiger, 1929, chap. 12, p. 271.

7. Kaufmann, J., and Gottlieb, R.: Innervation of Renal Parenchyma; Study to Demonstrate Nerve Endings in Renal Epithelium, Am. J. Physiol. **96**:40, 1931.

which they ascribed a secretory function. An autonomic sensory function may further be inferred from the successful relief of renal pain by denervation, as demonstrated by S. H. and R. G. S. Harris [8] and others. Ellinger and Hirth [9] presented evidence for a somewhat more complicated nervous function in the form of selective excretion influenced by various elements in the renal nerve supply. Studies of the renal function following denervation in the normal animal were made by Milliken and Kare,[10] de Gironcoli,[11] Caldwell, Marks and Rowntree,[12] Seres [13] and many others. All, except Seres, agreed that denervation results in at least a temporary increase in renal activity, followed by a return to a normal state in from two to five months. Seres stated that renal denervation is followed by renal insufficiency. This conclusion, however, is adequately contradicted by the other workers. S. H. and R. G. S. Harris performed renal denervation in twenty-eight patients, with no ill effects. We have not seen any evidence of injury to the kidney in observations on dogs lasting over a period of eight months. Extensive histologic and functional studies on denervated kidneys have been published. There is, however, little or no information available concerning the response of the denervated kidney to various insults as compared to the intact kidney, especially of the vascular bed under such conditions, and we therefore present the results of the experiments detailed in the following pages with this object in mind. Milliken and Kare noted that the function of the normal kidney is inhibited by ether anesthesia while that of the denervated kidney is unaffected. S. H. and R. G. S. Harris performed a bilateral denervation in one case of essential hematuria and in a second case of parenchymatous nephritis, with reported satisfactory results.

DENERVATION

Dogs were used throughout, and all operative procedures were performed under ethyl barbiturate anesthesia (Nembutal-Abbott).

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8. Harris, S. H., and Harris, R. G. S.: Renal Sympathetico-Tonus and Renal Sympathectomy, Canad. M. A. J. **24**:235, 1931.

9. Ellinger, P., and Hirth, A.: Function of the Renal Nerves, Arch. f. exper. Path. u. Pharmakol. **106**:135, 1925.

10. Milliken, L. F., and Kare, U. G.: The Influence of the Nerves on Kidney Function in Relation to the Problem of Renal Sympathectomy, J. Urol. **13**:1, 1925.

11. de Gironcoli, F.: The Denervated Kidney, Ztschr. f. urol. Chir. **27**:266, 1929.

12. Caldwell, J. M.; Marks, H., and Rowntree, L. G.: Renal Function After Bilateral Denervation of the Kidney in Normal Dogs, J. Urol. **25**:351, 1931.

13. Seres, M.: Denervation of the Kidney, Rev. méd. de Barcelona **1**:220, 1925; abstr., Ztschr. f. urol. Chir. **17**:54, 1925.

Unilateral denervation (left) was performed through an infracostal incision. The kidney was delivered through the wound, the peritoneum was divided, and the fat and the areolar tissue about the hilus were stripped away. Usually several nerves could be demonstrated grossly, and these were divided. The perivascular sheath was stripped down, and the artery was further deprived of its externa by rubbing between the blades of the hemostat. The kidney was returned to its normal position and the wound closed. Recovery to normal was then permitted for several weeks before experiments were made.

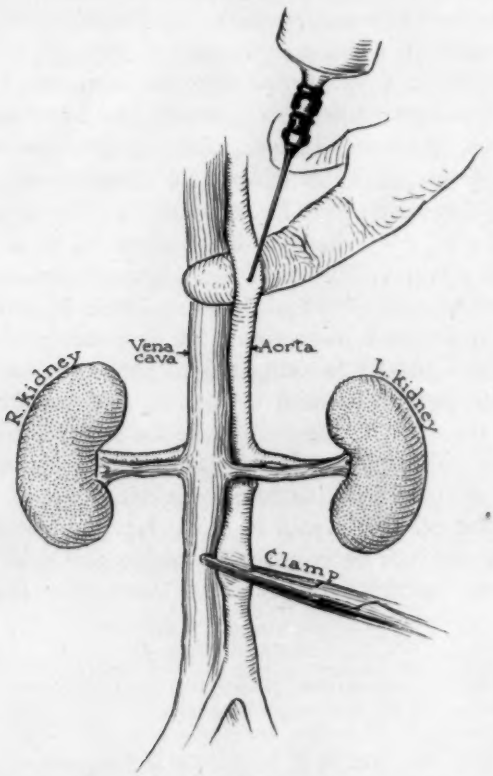

Fig. 1.—A diagram indicating the point of injection into the aorta relative to the position of the renal arteries.

ROENTGENOGRAPHIC DEMONSTRATION OF VASCULAR BED

A 25 per cent suspension of bismuth oxychloride in water was injected into the vascular bed of the kidney. It has been our experience that this mixture gives better results in antemortem injection than the acacia-bismuth oxychloride mixture recommended by Hill[14] for

14. Hill, E. C.: A Radio Opaque Bismuth Suspension for Anatomical, Histological and Pathological Research, Bull. Johns Hopkins Hosp. **44**:248, 1929.

postmortem injection. The technic of the injection was as follows (fig. 1):

The aorta was exposed through a left paravertebral incision. In order to obtain a good exposure, the last rib was removed, and occasionally the crus of the diaphragm was divided. The aorta was occluded below the origin of the renal vessels, and 50 cc. of a 25 per cent suspension of bismuth oxychloride was injected into the aorta above the origin of the renal arteries. The kidneys were removed from three to five minutes after the injection and bisected, and roentgenograms were made, a low voltage (60 volts) and a low milliamperage (5 milliamperes) being used, with an exposure of from four to five seconds.

THE VASCULAR BED IN THE DENERVATED KIDNEY

In normal kidneys in normal animals, the pictures obtained of the vascular bed are fairly uniform, as indicated in figure 2. It will be

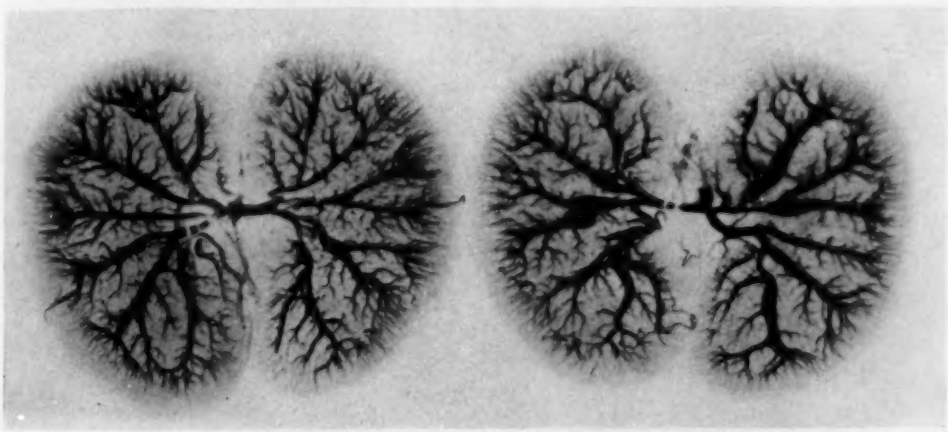

Fig. 2.—The renal vascular beds of a young normal dog after the injection of bismuth. Note the uniformity of extent and distribution of the arcuate and interlobular blood vessels.

noted that while there is some slight difference in the degree of injection shown by the large blood vessels on the two sides, the arcuate arteries and the arteria recti show a uniform and equal injection of bismuth for a distance of about three quarters of the width of the cortex. It will be further noted that the outlines of the large vessels are regular.

In some instances there may be but little filling of the large vessels with the material injected, although here again the fine vessels show a uniform and equal injection on the two sides.

In contrast with this uniform injection into the vascular tree in the normal kidney, a distinct increase in the size and number of blood vessels showing injection is apparent in pictures obtained from denervated

kidneys. This change in the vascularity is apparent as early as forty-eight hours and persists for an indefinite period (lasting at least two months). The experiments described in the following paragraphs are typical of the series.

Dog 1 (fig. 3).—The left kidney was denervated on April 4, 1930, and bismuth was injected into the renal vascular bed and roentgenograms were made two days later. The marked increase in the vascular bed demonstrated is associated with an increase in the size of the denervated (left) kidney. In microscopic sections, the only apparent difference is an increase in the size and the number of blood vessels and in the amount of contained blood in the denervated (left) kidney.

Dog 2 (fig. 4).—The left kidney was denervated on June 23, 1930, and bismuth was injected into the renal vascular bed eighteen days later. In spite of injury

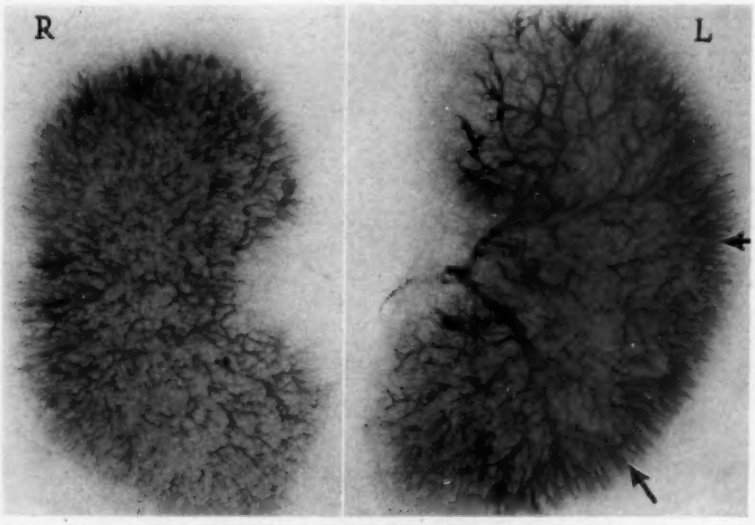

Fig. 3 (dog 1).—The left kidney was denervated forty-eight hours prior to the injection of bismuth into the vascular beds. Note the general vascular dilatation and particularly the large size of the arteria recti and their more marked projection to the margin of the cortex.

to the kidney in the course of the operation, the vascular bed was more widely dilated and the blood vessels were more abundantly demonstrated in the left kidney than in the right. There was no difference in the size of the two kidneys. These differences were especially well demonstrated in a thin section of kidney as seen in figure 6. The microscopic picture corresponded closely to that seen in the previous animal.

Dog 3 (fig. 5).—Dog 3 was old, being probably 8 or 9 years of age. The kidneys were grossly scarred and firm in consistency. The left kidney was denervated on Aug. 10, 1930. Bismuth was injected into the renal vascular bed two months later. The left kidney had increased considerably in size, weighing 42 Gm.; the right weighed but 30 Gm. The vascular beds of both kidneys showed evidence of serious damage, but that in the left was obviously more widely open

than that in the right. In microscopic sections of the right kidney there were areas, corresponding to the depressed scars on the surface, revealing the glomeruli atrophied, disintegrating or obliterated, with Bowman's space widely dilated and containing more or less clear, homogeneous exudate. In these areas, the tubules were poorly demarcated; their epithelium was shrunken and granular or entirely

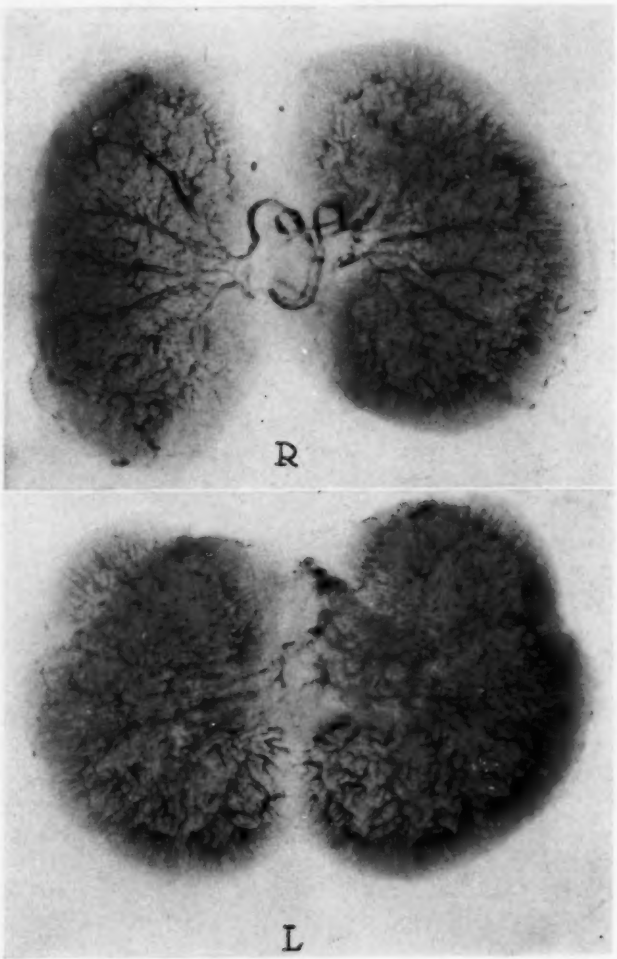

Fig. 4 (dog 2).—The left kidney was denervated on June 23, 1930. The roentgenogram shows the renal vascular beds eighteen days later, after the injection of bismuth.

lost. The lumina were small, and to a considerable extent the tubules were replaced by interstitial fibrous tissue. There was a diffuse interstitial round cell infiltration. Between these scarred areas the glomeruli were seen. The tubules were widely dilated, the epithelium was granular and shrunken, and a small amount of granular débris was present in the lumina. The blood vessels were of normal

dimensions, and the larger ones were well filled with the injected material. The left kidney presented the same appearance in the scarred areas, but in the intervening areas the glomeruli and tubules were much better preserved, and more injected material was seen in the finer vessels.

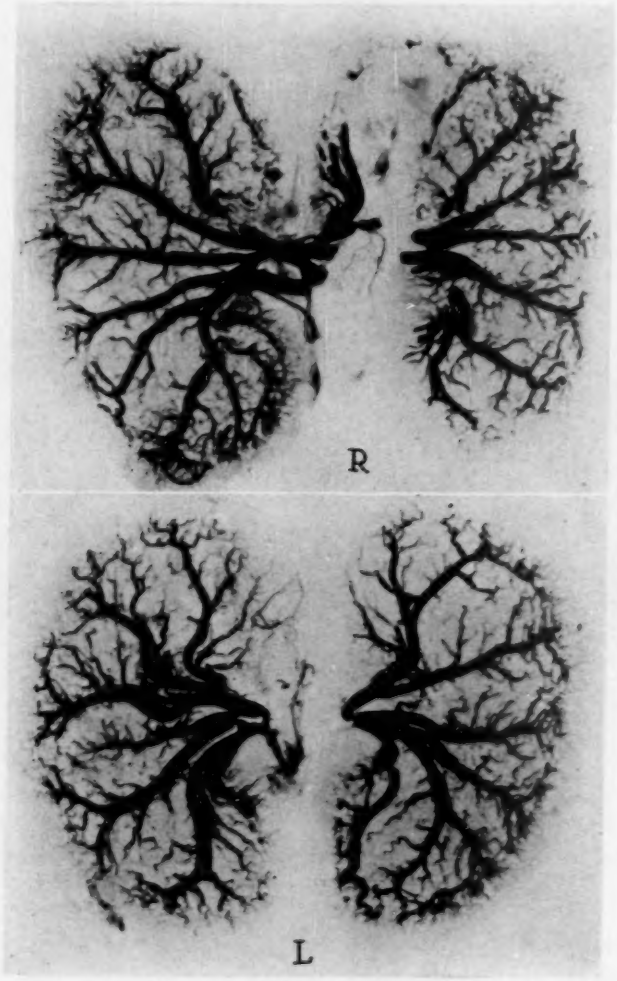

Fig. 5 (dog 3).—The left kidney was denervated on Aug. 10, 1930. The roentgenogram shows the renal vascular beds sixty-one days later, after the injection of bismuth.

Dog 4.—The left kidney was denervated on June 4, 1930. On August 20, 10 Gm. of iopax was injected intravenously, giving a shadow of the left pelvis only. The injection of bismuth into the kidney was unsatisfactory, but it nevertheless demonstrated a vascular bed rather wider open in the left kidney. The left kidney weighed 90 Gm.; the right, 65 Gm. Microscopically, the glomeruli of the

right kidney were of moderate size; the capillary loops were somewhat dilated and contained a few granules of injected bismuth but little blood. The tubular epithelium was rather granular, and the nuclei were pale. The blood vessels contained a moderate amount of bismuth and few blood cells. The glomeruli of the left kidney were larger than those of the right, and the dilated capillary tufts, as well as the interstitial blood vessels, were distended with red cells. The tubular epithelial cells showed rather more evidences of degenerative changes, and hyaline plugs were numerous in the lumina.

EFFECT OF EPINEPHRINE

A single injection of epinephrine was made into each of several normal and denervated dogs, and in each case bismuth was injected into the renal vascular bed in order to compare, in the vascular spasm obtained, the effectiveness of the denervation.

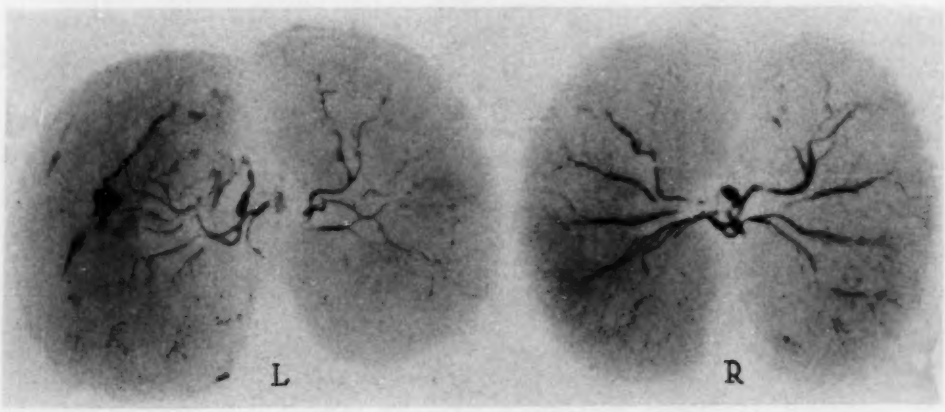

Fig. 6 (dog 5).—The vascular beds of normal kidneys after 2 cc. of a 1:10,000 dilution of epinephrine had been injected into the left renal artery followed by the injection of bismuth into both kidneys a few minutes later.

Dog 5 (fig. 6).—Two cubic centimeters of a 1:10,000 dilution of epinephrine was injected into the left renal artery of a young, normal dog. Very quickly general systemic effects were noted, and bismuth was injected into the kidneys. Grossly both kidneys were pale. The roentgenogram demonstrated obliteration of the small and medium-sized blood vessels in the left kidney, with a less marked effect in the right kidney. Microscopically, the glomeruli in the right kidney were uniformly distended, their capillary tufts were filled with erythrocytes, and bismuth granules were seen in many. The tubular epithelium was slightly granular. The blood vessels were distended with cells and bismuth.

In the left kidney, the glomerular capillaries contained much less blood and no granules of bismuth, and the blood vessels of the parenchyma contained few erythrocytes and little bismuth.

The roentgenogram of the vascular bed into which bismuth had been injected, as well as the histologic picture, showed the local action of epinephrine to be on the blood vessels.

Dog 6 (fig. 7).—The left kidney of dog 6 was denervated on Sept. 16, 1930. On March 30, 1931, 5 cc. of a 1:10,000 dilution of epinephrine was injected into the aorta above the origin of the renal vessels. Three minutes later, bismuth was injected into the kidneys. In the right kidney, there was almost complete obliteration of the finer blood vessels. In the left kidney (with the exception of a few patches in which the finer vessels were obliterated), a practically normal vascular bed was found. In the microscopic section of the right kidney, the glomeruli were constricted and contained little blood, and few interstitial blood vessels were seen. The sections of the left kidney stood in marked contrast with this picture. The vessels were dilated and prominent, the glomeruli were large, their capillaries distended with blood, and much injected material had reached the glomeruli.

SNAKE VENOM

The effect of rattlesnake venom is that of a powerful vascular poison causing endothelial injury, vascular paralysis and interstitial

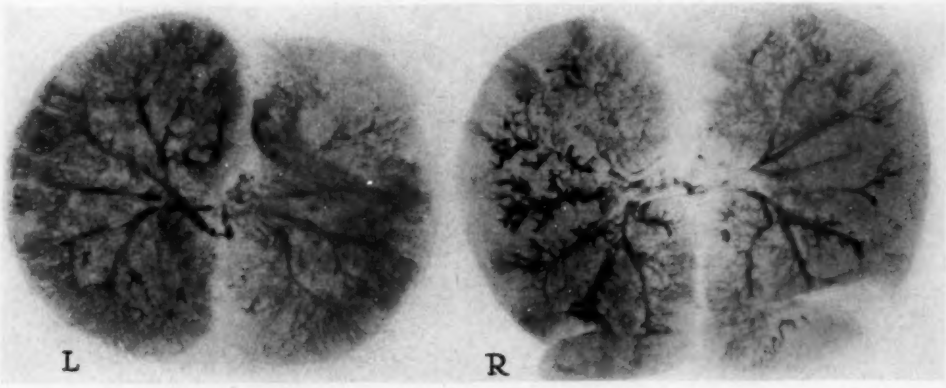

Fig. 7 (dog 6).—The left kidney was denervated on Sept. 16, 1930. Six and a half months later, 5 cc. of a 1:10,000 dilution of epinephrine was injected into the aorta above the origin of the renal arteries, followed a few minutes later by an injection of bismuth.

hemorrhages (Noguchi [15]). For this reason, we considered it of interest to determine the comparative effects of this material on the normal and the denervated kidney.

Dog 7.—Two tenths of a milligram of rattlesnake venom per kilogram of body weight was injected intravenously into a normal dog on Aug. 27, 1930, and bismuth was injected into the kidneys on Sept. 3, 1930. The roentgenogram demonstrated moderate beading of the large blood vessels; the small vessels were well preserved, and in the microscopic sections were seen moderate glomerular congestion and deeply stained, somewhat swollen tubular epithelium. The vessels were normal.

15. Noguchi, H.: An Investigation of Venomous Snakes with Special Reference to the Phenomena of Their Venoms, Washington, Carnegie Institute, 1903, vol. 141, p. 106.

Dog 8 (fig. 8).—Into a normal dog, 0.5 mg. of rattlesnake venom per kilogram of body weight was injected intravenously on Sept. 8, 1930. On September 16, bismuth was injected into the renal blood vessels after the urine from the two sides had been collected separately over a period of six hours. The volume of urine secreted on the right was 25.8 cc., and that on the left, 30.5 cc. The ammonia nitrogen in milligrams per hundred cubic centimeters was 83 on the right and 85 on the left. The x-ray picture demonstrated marked beading of the large vessels of both kidneys, with almost complete obliteration of the fine vessels.

Microscopic sections displayed marked congestion of the glomeruli with here and there hemorrhage or exudation into Bowman's space and swelling of the

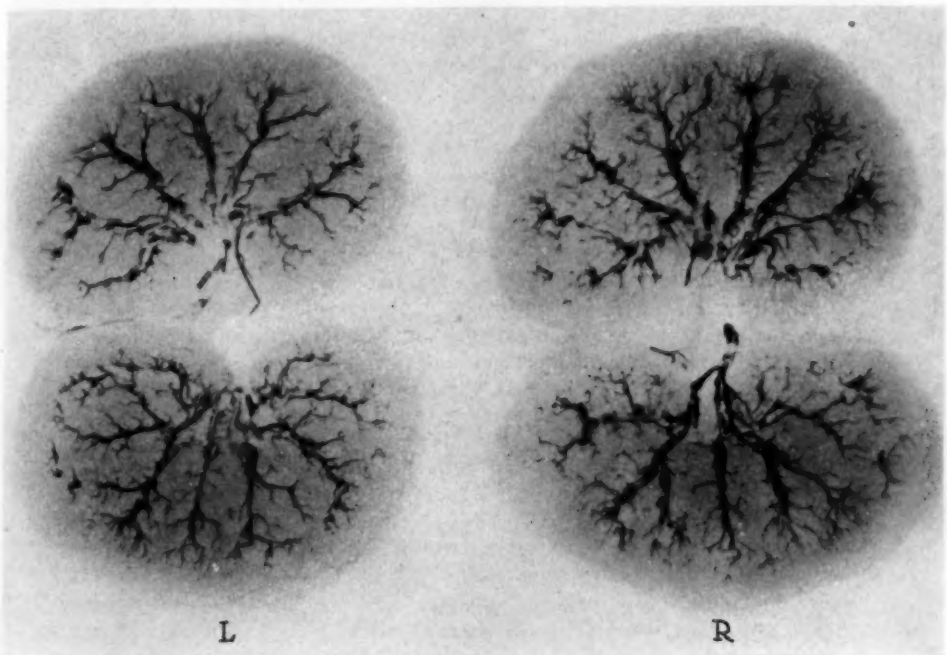

Fig. 8 (dog 8).—The vascular beds of intact kidneys eight days after the injection of 5 mg. of rattlesnake venom per kilogram of body weight, as delineated by an injection of bismuth on the eighth day.

capillary and arteriolar endothelium. The tubular epithelium was pale, swollen and granular, and the lumina contained much granular and hyaline débris.

Dog 9.—The left kidney was denervated on Sept. 19, 1930. On Dec. 23, 1930, 0.6 mg. of rattlesnake venom per kilogram of body weight was injected intravenously, and fifteen minutes later bismuth was injected into the kidneys. The entire left kidney showed an irregular injection of poor degree, with slight beading of the large blood vessels. The right kidney showed the large vessels well preserved, with a moderate decrease in the number of the small vessels that showed injection and in the degree of the injection.

Microscopically, the glomerular capillaries in the right kidney were moderately distended with blood, as were the interstitial capillaries and larger vessels. The

tubular epithelium was slightly swollen. Bismuth had penetrated to a few of the glomeruli and was found in small amounts in the larger vessels. In the left (denervated) kidney, the glomeruli were swollen and markedly congested, and their epithelial cells were swollen and pale. Here and there rupture with hemorrhages into Bowman's space was seen. The interstitial vessels were congested; the tubular epithelium was swollen and pale.

Dog 10.—The right kidney was denervated on Sept. 9, 1930. On Oct. 6, 1930, 1 mg. of rattlesnake venom per kilogram of body weight was injected intravenously. The dog died within twenty minutes, and bismuth was injected into the kidneys postmortem. The vascular beds in the two kidneys showed slight beading of the large blood vessels, with slightly less beading in the left. Microscopic sections, however, demonstrated more marked evidences of injury in the right kidney in the form of swelling of the tubular epithelium and marked congestion affecting particularly the glomeruli and interstitial blood spaces.

Dog 11.—The left kidney was denervated on Sept. 10, 1930. On Oct. 7, 1930, 0.5 mg. of rattlesnake venom per kilogram of body weight was injected intravenously. The dog went into profound shock, from which he recovered. On Oct. 8, 1930, the urine was collected separately from both kidneys for four hours. The left kidney secreted 19 cc. of urine, with a specific gravity of 1.036, and the excretion of ammonia nitrogen was at the rate of 38 mg. per hundred cubic centimeters. The right kidney in the same period secreted 13.5 cc. of urine, with a specific gravity of 1.038, and ammonia nitrogen at the rate of 29 mg. per hundred cubic centimeters. Bismuth was injected into the kidneys. The roentgenogram demonstrated a marked decrease in the finer vascular bed in the left (denervated) kidney, with a more mottled injection and some beading of the larger blood vessels. The right kidney displayed a practically normal vascular bed. Microscopically, the right kidney displayed a slight swelling of the glomerular endothelium, little blood in the capillaries, moderate interstitial edema and slight cloudy swelling of the tubular epithelium. Little injected material was seen in the smaller arterioles or glomeruli. In the left kidney, the glomerular endothelium was swollen; the capillaries were congested. The arteriolar endothelium was moderately swollen; the vessels contained considerable blood and bismuth. The tubular epithelium was the seat of marked cloudy swelling.

Dog 12 (fig. 9).—The left kidney was denervated on July 16, 1930. On Aug. 27, 1930, 0.5 mg. of rattlesnake venom per kilogram of body weight was injected, intravenously, and on Sept. 3, 1930, bismuth was injected into the renal vascular bed. The roentgenogram showed almost complete obliteration of the finer vascular bed of the left kidney with marked beading of the large vessels. In the right kidney, the finer vessels were well preserved and there was moderate beading of the larger vessels.

Microscopically, the glomeruli of the left kidney were markedly distended with blood, as were the interstitial blood spaces and blood vessels. The tubular epithelium displayed marked swelling in patchy areas, with deeply stained, granular appearing cytoplasm, and but little lumen was demonstrable. In the intervening areas, the tubular epithelium was vacuolated and broken down. In the right kidney, the evidences of injury were much less marked.

Dog 13.—The left kidney was denervated on July 16, 1930. On Aug. 20, 1930, 0.5 mg. of rattlesnake venom per kilogram of body weight was injected intravenously. On Sept. 5, 1930, bismuth was injected into the kidneys, and the roentgenograms demonstrated moderate diminution of the vascular bed of the left kidney, with slight beading of the larger blood vessels and a practically normal vascular bed of the right kidney.

Dog 14.—The left kidney was denervated on Sept. 5, 1930. Three days later 0.6 mg. of rattlesnake venom per kilogram of body weight was injected intravenously. This was followed by a severe reaction with marked vomiting. On Sept. 18, 1930, bismuth was injected into the kidneys. The larger blood vessels showed marked beading. There was a somewhat better injection into the fine vessels on the left than on the right.

Dog 15.—The left kidney was denervated on May 27, 1930. Five months later, 1 mg. of rattlesnake venom was injected intravenously, and after a period of twenty minutes bismuth was injected into the renal vascular bed. The filling of the blood vessels of the left kidney was demonstrated in the roentgenogram to be poor and patchy; the vessels were narrow and constricted. In the right

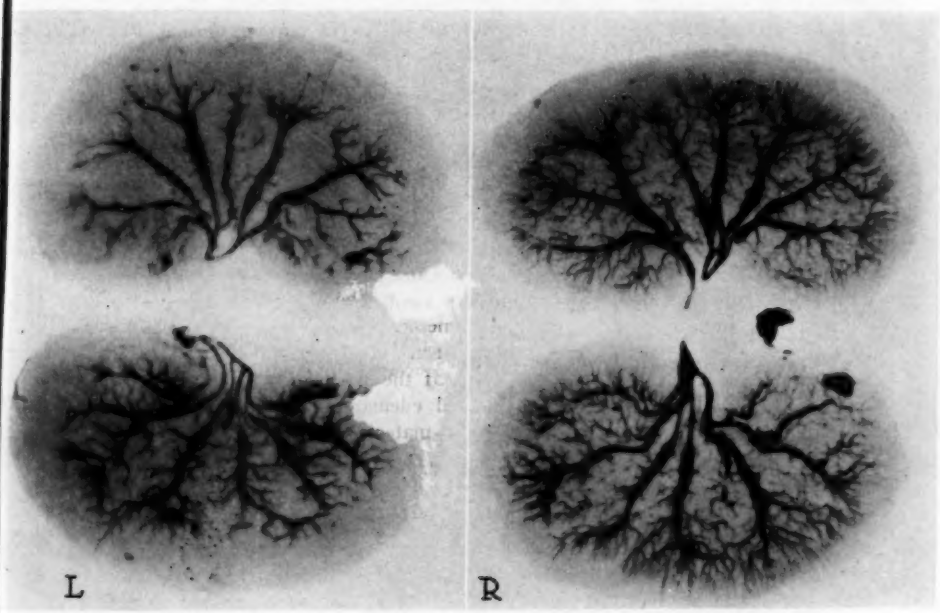

Fig. 9 (dog 12).—The left kidney was denervated on July 16, 1930. One month later, 0.5 mg. of rattlesnake venom per kilogram of body weight was injected intravenously. The roentgenogram shows the vascular beds one week later, following an injection of bismuth.

kidney, however, the large vessels were well preserved, and though the finer vessels showed a poor injection of bismuth they were demonstrated much better than in the left kidney.

Microscopically, the right kidney displayed marked swelling and congestion of the glomeruli, marked swelling of the interstitial blood vessels and a few interstitial hemorrhages. The endothelium of the arterioles was swollen. The tubular epithelium was swollen and granular.

The glomeruli of the left kidney were even more markedly swollen, almost uniformly obliterating Bowman's space. The same endothelial swelling of the arterioles was seen here as on the right, with the same vascular congestion. However, swelling of the tubular epithelium was much more marked, especially in the convoluted tubules, where the lumen was almost obliterated.

CHILLING

A group of dogs was subjected to low temperatures for varying periods of time; bismuth was injected into the renal vascular bed, and subsequently roentgenograms were made to determine the changes in the blood vessels. The animals were shaved over the trunk, anesthetized and packed in ice for the desired length of time.

Dog 16.—A normal dog was chilled for one hour. Bismuth was injected into the kidneys, and roentgenograms demonstrated a wide vascular bed with the arteria recti extending almost to the outer margin of the cortex.

Dog 17.—Dog 17 was treated exactly the same as dog 16. During the time of chill lasting one hour, no urine was secreted from either kidney. At the end of this period, bismuth was injected into the kidneys, and a normal bed was demonstrated.

Dog 18 (fig. 10).—The dog was denervated on June 9, 1931. Two weeks later, the animal was chilled for ten minutes, and bismuth was injected into the kidneys. The cortical vascular bed of the left (denervated) kidney showed extensive injection, while that of the right was but poorly delineated. The left kidney weighed 38.5 Gm., while the right weighed 29.5 Gm.

Microscopically, the capillaries of the glomeruli and the interstitial vessels contained little blood or bismuth, and the tubular epithelium was pale and shrunken in the right kidney, whereas in the left kidney the vessels were all distended with blood, and the tubular epithelium was swollen and deeply stained.

Dog 19.—The left kidney was denervated on Oct. 29, 1930. On November 16, the region of the kidneys was shaved and ice applied locally for twenty minutes. Bismuth was then injected. The vascular bed of the left kidney showed somewhat better injection than that of the right kidney. The difference, however, was not marked.

On microscopic section, the glomeruli of the right kidney were of moderate size, and their capillaries contained a moderate number of red cells. The tubular epithelium appeared normal; the interstitial blood vessels contained a moderate amount of blood. In the left kidney, the glomeruli were larger, their capillaries contained much more blood, and granules of bismuth were found to have penetrated many of them. The interstitial vessels contained more blood than those in the right kidney; the tubular epithelium was rather well preserved.

Dog 20.—The left kidney was denervated on June 28, 1930. On July 23, an ice pack was applied for one hour, during which the right kidney secreted 10.5 cc. and the left 9 cc. of urine with a specific gravity of 1.040 and 1.038 and an ammonia nitrogen content of 31 and 29 mg. per hundred cubic centimeters, respectively. Injection at this time showed a more widely open vascular bed in the left kidney, with considerably better injection into the finer vessels.

Microscopically, the glomerular capillaries in the right kidney were rather markedly dilated and contained little blood, although the granules of bismuth had penetrated into many of them. The blood vessels and tubules were essentially normal. In the left kidney, the glomeruli were distended with blood, and here again granules of bismuth had penetrated to the capillary loops. The interstitial vessels contained a considerable amount of blood, and the tubular epithelium was well preserved.

Dog 21.—The left kidney was denervated on Sept. 30, 1930, and the injection of bismuth was made on November 5. The animal was chilled for one and one-

half hours. The roentgenogram showed marked obliteration of the vascular bed in each kidney, more marked in the left.

Microscopic section of the right kidney displayed moderate congestion of glomerular capillaries and interstitial blood vessels. The tubular epithelium was moderately swollen, pale and vacuolated. The section of the left kidney displayed normal glomeruli and about the same degree of tubular degeneration as was seen

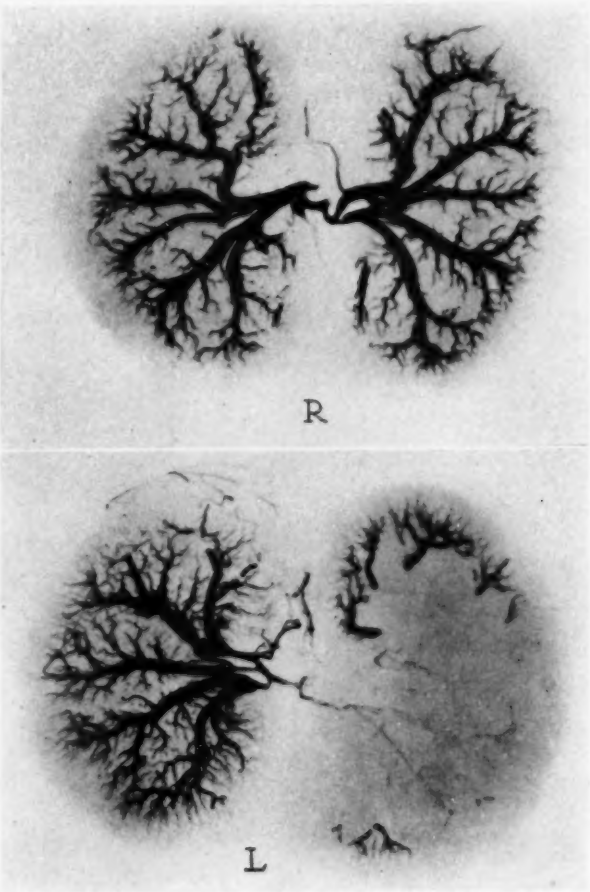

Fig. 10 (dog 18).—The left kidney was denervated on June 9, 1931. Two weeks later, ice was applied over the kidneys for ten minutes, and then bismuth was injected into the renal vascular beds. One branch of the left renal artery was occluded during the injection, so that a poor injection was obtained in the corresponding half of the kidney.

in the right kidney. The injected bismuth had penetrated the finer vessels, and fragments were seen in the glomerular tufts.

After a short period of chilling, it appeared that the vascular bed of the normal kidney was constricted as a result of a spasm of the

small vessels, while the vascular bed of the denervated kidney showed little change. With a longer period of chilling, however, the result was variable, and in many cases the vascular beds of both kidneys were dilated.

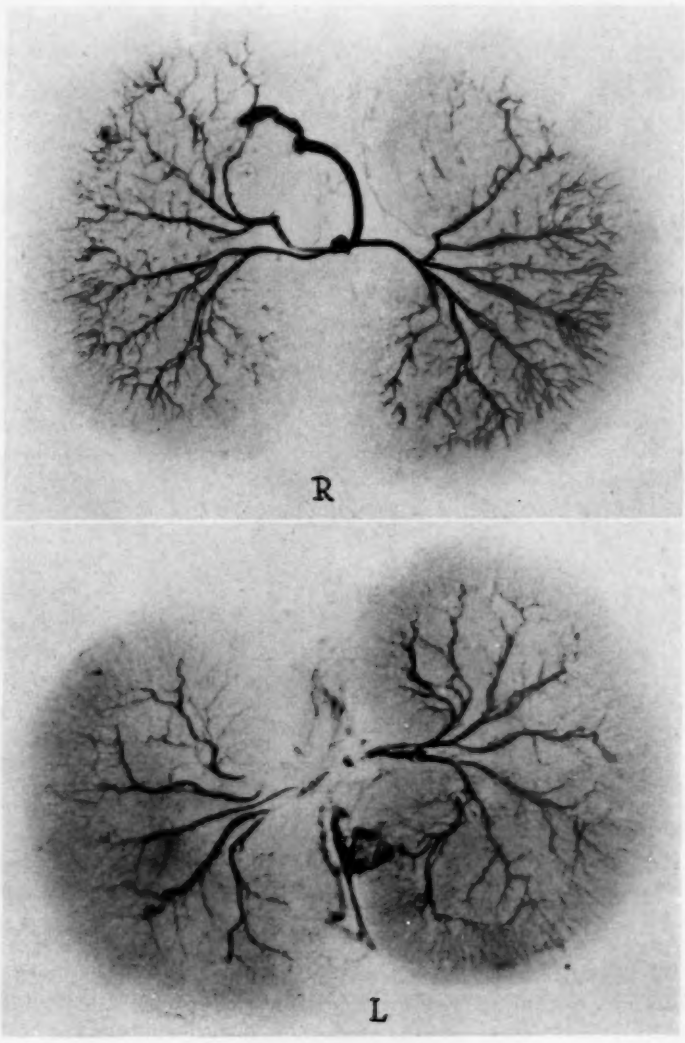

Fig. 11 (dog 22).—The left kidney was denervated on Oct. 9, 1930. Two weeks later, daily chilling was begun and continued for eleven weeks. Then bismuth was injected into the renal vascular beds.

REPEATED CHILLING

A group of animals were subjected to daily chilling for a period of from two to six months. The animals were placed in an ice chest after

having been shaved and daily subjected to a temperature of about 0 C. for a period gradually increasing from five minutes to an hour.

Dog 22 (fig. 11).—The left kidney was denervated on Oct. 9, 1930. Daily chilling was begun on October 20. Bismuth was injected on Jan. 7, 1931. The kidneys were found to be equal in size and showed good injection. The left kidney showed a cortical vascular bed of much more marked extent than the right.

Histologic sections of the right kidney showed the glomeruli to be distended, the capillary loops filled with blood and containing granules of injected bismuth. In a few, the endothelium of the afferent vessels was swollen, and occasionally hemorrhage into Bowman's space was seen. The arterioles displayed some swelling of their endothelium. The tubular epithelium was swollen and granular, and considerable granular and hyaline débris was present in the lumina. In the left kidney, the glomeruli presented a normal appearance and contained many fragments of the bismuth. Bowman's space was everywhere free from contents. The tubular epithelium was everywhere well preserved.

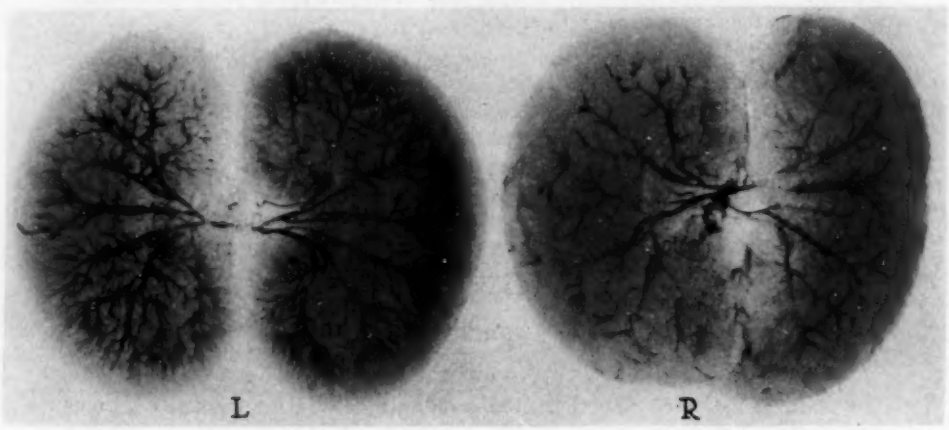

Fig. 12 (dog 23).—The left kidney was denervated on June 11, 1930. One week later, daily chilling was begun and continued for three months. Then bismuth was injected into the renal vascular beds.

Dog 23 (fig. 12).—The left kidney was denervated on June 11, 1930. Daily chilling was begun on June 18, and on September 12 the urine was collected separately from both kidneys, and bismuth was then injected into the kidneys. The vascular bed of the left kidney was normal, while that of the right kidney was almost completely obliterated. The left kidney weighed 33.5 Gm. and the right kidney, 27 Gm.

Microscopically, the histologic section of the right kidney demonstrated marked dilatation and congestion of the glomerular capillaries, as well as of the interstitial blood vessels. The tubular epithelium was swollen and granular in some areas, and in others it was shrunken and broken down. Considerable granular débris was present in the tubular lumina. The sections of the left kidney showed evidence that the congestion was much less marked than in the right, not only in the glomeruli, but also in the interstitial vessels. The tubular epithelium was somewhat better preserved than that in the right kidney.

Dog 24.—The left kidney was denervated on June 11, 1930. The daily chilling was begun on June 18, and bismuth was injected into the kidneys on July 21. The vascular bed of the left kidney was found to be practically normal. In the right kidney there was practically no injection of bismuth into the finer vessels, and there was slight beading of the larger vessels.

Dog 25.—The left kidney was denervated on June 11. Daily chilling was begun on June 18. On September 9, the dog died. The cause of death was pneumonia. The roentgenogram of the vascular beds of the kidneys showed evidences of marked injury. The left, however, was far better preserved than that of the right kidney. There was some evidence of beading in the large blood vessels of both kidneys.

In the microscopic section of the right kidney, the glomeruli were slightly congested. The endothelium of the afferent vessels was swollen, and occasionally granular débris or erythrocytes were seen in Bowman's space; little bismuth had reached the glomeruli. The tubular epithelium was well preserved. The section of the left kidney showed that the congestion of the glomeruli was more marked. The tubular epithelium was swollen and more granular; otherwise, the picture was the same as in the right kidney.

Dog 26.—The left kidney was denervated on Sept. 24, 1930. Daily chilling was begun on October 20, and bismuth was injected into the kidneys on March 30, 1931. There was practically no difference in the vascular beds on the two sides nor was there any marked change. Microscopically, the histologic section of the right kidney showed a marked congestion and dilatation of the glomerular capillaries, with slight swelling of the vascular endothelium in both the capillaries and the arterioles, and marked cloudy swelling of the tubular epithelium. In the left kidney, the picture was essentially the same, except that evidence of congestion was not as marked, and endothelial changes in the blood vessels were not seen.

COMMENT

By means of these roentgenologic studies of the vascular bed of the kidney we have demonstrated a definite dilatation of the vascular bed following denervation, which, persisting for at least two months, is in agreement with the microscopic findings of de Gironcoli. In an old animal having renal lesions best classified as chronic nephritis, we have demonstrated an increase in the size of the organ, as well as in its vascularity, following denervation.

To determine the efficacy of the denervation, epinephrine was used; in the normal dog, it was found to cause an obliteration of the renal vascular bed, but in the unilaterally denervated animal, the denervated kidney was found to be practically unaffected. This is of importance in that it demonstrated the effectiveness of the denervation that we had achieved.

In a small group of animals to which mercuric bichloride was administered, no change in the vascular bed was demonstrable. Repeated doses of uranium similarly showed no effect. Further work with these metallic poisons is now under way.

In the response to the injection of a vascular poison, such as rattlesnake venom, the normal and denervated kidneys showed marked differences so far as the toxic effect was much more marked on the denervated kidney. This was apparent in the obliteration of the cortical vascular tree in the roentgenogram, as well as in the microscopic observations. We deal here with the probability that the response of the normal kidney involves a prompt vasoconstriction. The denervated kidney, unable to protect itself, receives the bulk of the toxic material and is more severely injured. Cortical edema then results, and this in turn leads to the obliteration of the lumen of the smaller blood vessels of the cortex, while corresponding vessels of the intact kidney retain their normal size.

That this same relation seems to be operative with infectious processes might be evident from an examination of normal and denervated kidneys in animals that have died from distemper (dogs 6517, 6124 and 6038). In these cases, too, the denervated kidney shows greater change than the normal kidney.

In examination of the roentgenograms of these kidneys, we would stress particularly the importance of the degree of injection shown by the cortical vessels rather than the changes that are observable in the larger vessels of the kidneys. Localized constrictions or beadings similar to those demonstrated by Graham [16] in human arteriosclerotic kidneys were observed to occur spontaneously in the kidneys of old dogs, as well as following injections of rattlesnake venom and after repeated chilling. In the old animals, they are probably due to focal sclerotic change in the vessels. Following the injection of rattlesnake venom and repeated chilling, they are ascribable to the swelling of the intima seen microscopically and possibly to localized areas of vasomotor spasm.

Of special importance to us were the results obtained by repeated chilling of animals daily over a period of months, because we presumably deal here with the result of a purely autonomic effect.

Maintenance of the functional normality of individual organs or of an organism as a whole involves constant autonomic vascular adjustment. While this is accepted as axiomatic in the consideration of physiologic problems, it is not infrequently overlooked in investigations in the pathologic field, where we are apt to concentrate our attention on a presumptive exogenous pathogenic factor rather than on the failure of organic adjustment.

This is true even for resistance to infection. The herpes virus affords a striking example. Constantly present about the labial and

16. Graham, R. S.: A Study of the Circulation in the Normal and Pathological Kidney with Roentgenographic Visualization of the Arterial Tree Including the Glomeruli, Am. J. Path. **4**:17, 1928.

nasal orifices in certain persons, it gives rise to no pathologic lesion except at certain times (chilling, menstrual cycle, gastro-intestinal upset) when the vasomotor control of the skin is altered.[17]

This being true for the skin with its relatively small blood supply and low metabolic demand,[17] how much more important must be the proper autonomic coordination in organs of great metabolic demand such as the kidney?

We have been able to show that bacteria (B. coli), the intravenous injection of which is normally followed by the appearance of albumin, red blood corpuscles and casts (as well as of the bacteria) in the urine (and which therefore must be considered as exogenous toxic agents) do not bring about this pathologic effect if the autonomic innervation to the kidney (vasomotor control) is severed.[18] We have also shown that the chill associated with bacterial invasion is associated with vasoconstriction in the kidney, and we believe the assumption to be justified that the initiation of deranged function of the kidney under these conditions is predicated on two factors—autonomic dysfunction (relative ischemia of the kidney) *together with* an exogenous (and possibly an endogenous) toxic factor.

The effect of chilling offers a number of interesting problems. When the animal chills as the result of bacterial invasion, a peculiar muscular tremor occurs to which has been ascribed the increase in temperature that usually follows in its wake. As a matter of fact, we have demonstrated [19] that the muscular phenomenon is merely part of the autonomic reaction during which the peripheral vascular bed is contracted and the splanchnic bed (liver, spleen, gastro-intestinal tract) is dilated. It is, of course, associated with the entrance of adrenal secretion in large quantities into the circulation.

When the chill is induced by external cold, a similar effect takes place in the splanchnoperipheral balance. But when the chill is severe and prolonged, this autonomic balance is disturbed, and even the vascular bed of the kidney becomes dilated. The roentgenograms of the kidneys of animals chilled for short periods of time or following local applications of ice to the peripheral tissues show a distinct difference in the effect on the denervated, as compared with the normal, kidney, the denervated kidney being relatively vascular. With prolonged and fatal exposure, this difference is no longer apparent.

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17. Petersen, W. F., and Levinson, S. A.: The Skin Reaction, Blood Chemistry and Physical Status of Normal Men and Clinical Patients, Arch. Path. **9**:151, 1930.

18. Milles, G.; Müller, E. F., and Petersen, W. F.: Studies in Renal Denervation, Proc. Soc. Exper. Biol. & Med. **28**:351, 354 and 561, 1931.

19. Müller, E. F., and Petersen, W. F.: Ueber das Verhalten der Skelett-Muskulatur in Schüttelfrost, München. med. Wchnschr. **74**:1218 and 1276, 1927.

These experiments would indicate that in the normal kidney a vasoconstrictor effect occurs during the time of a short chilling and make it probable that the urinary changes that are found under such conditions (albumin, red blood cells, casts, etc.) are in part the result of temporary ischemia. In an autonomically labile person, they would naturally be more pronounced than in a normal person.

We have the impression, too, that the association of chilling with the onset of acute nephritis is of pathogenic importance. Under such conditions, the renal tissue, with its relative ischemia, is apparently more readily damaged than when the vascular supply is adequate.

The constriction associated with an acute chill in the onset of nephritis may be the factor determining whether or not the damage produced by an infectious agent will be sufficiently great to become permanent or whether it will be merely transient.

In the consideration of the causative factors that are involved in the complicated pictures of chronic nephritis, hyperpiesis and the more acute forms that are found in the arteriolosclerotic types, autonomic dysfunction with repeated arteriolar spasm has been suggested. Jaffe,[20] for instance, presented histologic evidence that makes very probable a relationship of repeated arteriolar spasm of the afferent arterioles of the glomerulus to the pathologic picture of the arteriolosclerotic kidney. Kylin [21] discussed the presumptive instability of the autonomic status of such patients, as well as characteristic peculiarities of their blood chemistry.

So, too, the "wear and tear of modern life" must involve greater demands on the autonomic apparatus and produce autonomic maladjustment leading directly or indirectly to vasomotor dysfunction in susceptible organs.

Repeated chilling producing such a spasm, when involving blood vessels of the kidney, may finally bring about anatomic changes. In our experiments in which dogs were chilled daily over long periods of time, a distinct difference was found rather uniformly and regularly involving particularly the finer vessels, those in the normal kidney being practically obliterated, while those in the denervated kidney remained unaffected.

In view of these pronounced changes that have resulted from such repeated spasms of the renal vessels it seems logical to assume that these must play some rôle in the production of certain types of nephritis.

The interpretation of the results of a histologic examination of the kidneys of dogs always offers certain difficulties. It has been recog-

20. Jaffe, R. H.: Vascular Changes of Kidney in Hypertension, Am. J. M. Sc. **169**:88, 1925.

21. Kylin, E.: Die Hypertoniekrankheiten, Berlin, Julius Springer, 1926.

nized that fat, for instance, is almost always a normal constituent in the tubular epithelium and other apparent, degenerative changes in the tubular epithelium occur so constantly as to be without significance unless extremely marked. On the other hand, it is unusual to observe definite changes in the glomeruli or in Bowman's capsule. In this series, we observe normally moderate vascular dilatation following denervation, such as was seen by de Gironcoli, a variation in the penetration of the injected material into the finer blood vessels and particularly into the glomerular capillaries. This penetration of injected material was only roughly estimated, but usually it was found to be more marked in the denervated than in the normal kidneys. Eppinger [22] observed a marked decrease in the penetration of india ink following injury with mercuric chloride and took this as an indication of a diminution in the blood flow. Following the injection of snake venom, marked congestion and some interstitial extravasation of blood and red cells are seen in the tubules, especially in the denervated kidneys. After repeated daily chilling, marked congestion and some endothelial swelling of the arterioles and capillaries are found in normal kidneys as compared with the usual picture seen in denervated kidneys.

CONCLUSIONS

As shown by roentgenologic study of the vascular bed of the kidney in dogs, renal denervation is followed by a long persisting dilatation of the cortical blood vessels.

Chilling of the animal for a short period of time causes a definite vasoconstriction of the intact kidney as compared with the denervated organ; with prolonged and fatal chilling, this difference is no longer apparent. Daily chilling over long periods of time results in marked change of the vascular bed of the normal kidney, while the denervated kidney remains unaltered. A relation of the chill to the onset of acute nephritis, as well as of the effect of repeated spasm of the renal vessels (as with repeated chilling) to the pathogenesis of nephritic changes is made probable.

A vascular poison, such as snake venom, causes greater injury to the denervated kidney, the normal kidney presumably protecting itself through vasoconstriction. The effect appears to be true for infectious diseases as well (distemper).

No change in the vascular bed was observed with single doses of mercuric bichloride or with repeated doses of uranium acetate.

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22. Eppinger, H.; Laslo, D.; Rein, F., and Schurmeyer, A.: Circulatory Changes in the Pathological Kidney, Klin. Wchnschr. **9**:633, 1930.

EXPERIMENTAL INFARCTION OF THE GLOMERULI IN DOGS

II. BLOOD PRESSURE IN CHRONIC RENAL INSUFFICIENCY *

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In former years, the clinical and anatomic characteristics of those forms of Bright's disease that are associated with arterial hypertension were interpreted on the postulate that the changes in the kidneys were primary, and that, consequently, all clinical and anatomic alterations resulted from decrease in renal function. Gradually, however, a different concept has developed which conceives Bright's disease as a clinical and anatomic complex in which the renal damage is only part of a general disease such as occurs in arteriosclerosis, glomerulonephritis or essential arterial hypertension.

Crucial facts that would aid in evaluating these two divergent concepts should come from patients in whom death occurs from disease that affects only the kidneys, or from animals in which the kidneys alone are altered by experimental procedures. Chronic forms of renal insufficiency in which anatomic changes are localized to the kidneys are rare in human beings and, as a result, the usual conception of Bright's disease is derived from patients in whom many organs are simultaneously altered. Likewise, many of the experimental methods for studying Bright's disease can be objected to because the noxious substances used, even though they change the kidneys preponderantly, may affect many other tissues.

The majority of instances of human Bright's disease are combinations, clinically, of renal insufficiency, edema, arteriosclerosis, arterial hypertension and uremia. The pathologist, particularly, is often confronted with anatomic inconsistencies in associating these alterations causally with a proportional decrease in renal tissue. He observes cases in which hydronephrotic atrophy induces death, and he may not find hypertrophy of the left ventricle, arteriosclerosis or edema. On

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* From the Pathological Laboratory of the Presbyterian Hospital and the Norman Bridge Pathological Laboratory of Rush Medical College of the University of Chicago.

the other hand, he observes cases in which renal damage is not severe, yet arteriosclerosis, hypertrophy of the left ventricle and edema may be marked. It is on account of many of these inconsistencies that additional doubt has been introduced against the concept that renal damage alone explains all of the clinical and anatomic alterations observed in acute and chronic Bright's disease.

METHOD USED IN PRODUCING RENAL INSUFFICIENCY

Miller and Apfelbach[1] described a method of producing chronic renal insufficiency that alters only renal tissue, thereby avoiding some of the criticism advanced against experimental methods in which tissues other than the kidneys might also be damaged. By their method, infarction of glomeruli follows the injection of a suspension of charcoal particles into the renal arteries, the particles being of such size that they occlude the lumina of the glomerular capillaries. This method of inducing chronic renal insufficiency was chosen because of the following factors:

1. The interference with renal function is a direct result of the experimental procedure, and no other changes in the body result except the healing of the surgical incisions through the wall of the body in the lumbar regions.

2. The renal insufficiency is comparable to that which occurs in human beings, namely, retention of nitrogenous end-products in the blood plasma, fixation of the specific gravity of the urine and excretion of albumin and casts in the urine.

3. The renal insufficiency is chronic. Some dogs have lived for several months.

4. It has been suggested by some experimenters that, in order to secure an elevation of blood pressure in experimental Bright's disease, the reduction of kidney tissue must be accomplished in such a manner that the destroyed tissue is left in situ. The method described by Miller and Apfelbach meets this objection to the excision method of producing renal insufficiency, for the retrogressive changes that result in the glomeruli and convoluted tubules subsequent to infarction resemble the changes observed in human chronic Bright's disease.

The authors concluded that there is a constant syndrome characteristic of chronic renal insufficiency in dogs induced by gradual reduction of renal tissue. Also, in the course of this later study on blood pressure in relation to renal insufficiency, they have become even more impressed with the constancy of the clinical and anatomic alterations that are associated with what might be called "pure renal insufficiency." The following characteristics are always present and occur in direct proportion to the degree of reduction of renal tissue: (1) low and fixed

1. Miller, E. M., and Apfelbach, C. W.: Arch. Path. 4:193, 1927.

specific gravity of the urine, (2) loss of flexibility in the capacity of the kidneys to vary the rate of excretion, (3) polyuria, (4) albuminuria, (5) casts, (6) retention of nitrogenous end-products in the blood, (7) decrease in the carbon dioxide-combining power of the plasma and (8) decrease in body weight.

On the other hand, some of the characteristics of human Bright's disease were never observed. Edema did not occur. Anemia was never severe and usually did not exist. Fatty change of the kidneys, so frequently found in subacute and chronic glomerulonephritis, was not encountered. Convulsions, muscular twitchings and stupor were not observed until the carbon dioxide-combining power of the blood reached a value of from 15 to 25 per cent.

MANOMETER USED IN STUDY OF BLOOD PRESSURE IN DOGS WITH RENAL INSUFFICIENCY

The relationship of arterial hypertension to experimental chronic renal insufficiency had not been definitely settled in the report by Miller and Apfelbach. They stated:

> We have tried to record the blood pressure by bands adapted to the thigh, but the results were so inconsistent in normal animals that no confidence is placed in them. Alterations in the weight of the heart are also difficult to interpret. We have attempted to arrive at a standard for the heart and body weight, but this also is too variable. The weight of the heart is apparently more dependent on the previous activity of the dog than on body weight. The variations in thickness of the papillary muscles and trabeculae carneae are also not usable.

For the purpose of studying the blood pressure in dogs with renal insufficiency, we [2] designed a mercury manometer that could be used daily without anesthesia. A 22 gage needle in the femoral artery distal to Poupart's ligament connects the blood stream with a mercury manometer. Only a mean systolic pressure can be obtained, but this mean systolic pressure is only a few millimeters lower than the mean systolic pressure obtained simultaneously in the femoral artery through a large glass cannula. The error in this method is a constant one, whereas our experience with cuff methods was such that no constancy of determinations could be obtained. For the purpose, therefore, of recording permanent alterations in the mean systolic blood pressure, we believe that this method is a reliable one.

THE PROBLEM OF THE RELATIONSHIP OF EXPERIMENTAL RENAL INSUFFICIENCY TO BLOOD PRESSURE AS RECORDED IN THE LITERATURE

The conclusions arrived at by experimenters concerning the relationship of arterial hypertension to renal insufficiency are as inconsistent

2. Jensen, C. R., and Apfelbach, C. W.: Arch. Path. 6:99, 1928.

as are those entertained by clinicians. Passler and Heincke [3] studied the blood pressure after removing portions of renal tissue in dogs. Ether anesthesia was used, and a cannula was inserted into the femoral artery and attached to a mercury manometer. When 50 per cent of the kidney had been removed, they found polyuria, an elevation of blood pressure of from 15 to 29 mm. of mercury, and hypertrophy of the wall of the left cardiac ventricle in 29 per cent of their animals.

Janeway,[4] using dogs, excised one kidney and tied off branches of the renal artery of the other kidney. Some of the dogs lived from thirty-nine to one hundred and sixty-three days. A Riva-Rocci cuff was used in making the blood pressure observations. An elevation of blood pressure in several animals was recorded, the highest being 37 mm. of mercury.

Backmann,[5] using a Trendelenburg tonometer, found no changes in blood pressure after bilateral nephrectomy, but after removal of one kidney and a small piece of the other, he noted a rise of 18 mm. of mercury.

Anderson,[6] using rabbits, made determinations of blood pressure from the central artery of the ear. All of one kidney and part of the other were removed, about 70 per cent in all. The animals lived from one hundred to two hundred days after the operation. Two of the rabbits apparently died from renal insufficiency; others had a moderate degree of renal insufficiency, and some were recovering. None showed a rise of blood pressure.

Cash,[7] in a series of ten dogs, using several different operative procedures, came to the following conclusions: 1. A rise of systolic and diastolic pressures in most instances and a rise of diastolic pressure in all is obtained when a reduction of at least 50 per cent of the renal substance is effected, provided a portion of renal tissue that has been deprived of its circulation is allowed to remain in situ. 2. Either removal of one kidney alone or infarction of one kidney alone is without effect on the blood pressure. 3. The increase in blood pressure reaches its height within a few days following operation, after which it tends to return to normal. Cash made his observations on blood pressure by means of a Kolls metal cuff together with a mercury manometer and a sphygmograph, and he continued to record them for from two to four months. Routine observations were also made on the nonprotein nitrogen and total chloride contents of the blood, with occasional determina-

3. Passler and Heincke: Verhandl. d. deutsch. path. Gesellsch. **9**:99, 1905.

4. Janeway, T. C.: Proc. Soc. Exper. Biol. & Med. **6**:108, 1908-1909; Am. J. M. Sc. **145**:625, 1913.

5. Backmann, E. L.: Ztschr. f. d. ges. exper. Med. **4**:63, 1914.

6. Anderson, H. C.: J. Exper. Med. **39**:707, 1924.

7. Cash, J. R.: Bull. Johns Hopkins Hosp. **35**:168, 1924.

tions of the blood creatinine, and on phenolsulphonphthalein excretion. It seems, though, that no marked degree of renal insufficiency was produced in any of his dogs.

A method of obtaining what might be fairly classified as pure renal insufficiency was reported by Hartmann, Bolliger and Doub.[8] They irradiated the kidneys of dogs in several ways. Acute and chronic changes were produced, including tubular degeneration, sclerosis of vessels and, finally, shrunken, sclerotic kidneys. Undoubted renal insufficiency was produced in those that survived, as measured by retention of blood metabolites, lowered carbon dioxide-combining power of the plasma and diminished phenolsulphonphthalein excretion. The authors stated: " . . . in the final stages systolic blood pressure reached 230 and the diastolic 150 in some instances."

Thus, it may be seen that experimental methods so far have not been in agreement as to the causal relationship between renal insufficiency and arterial hypertension.

OBSERVATIONS ON NATURAL ELEVATIONS OF BLOOD PRESSURE IN DOGS

During the course of our study of the blood pressure in dogs, we observed that there were fluctuations in the mean systolic pressure that seemed to be concomitant with changes in the temperature of the room. In order to confirm this observation, a room was constructed in which the temperature could be automatically regulated.[9] A continuously recording Tycos thermometer was installed that recorded the dry bulb and wet bulb temperatures. The carbon dioxide content of the room did not fluctuate appreciably. The observations were made on large dogs that had become accustomed to manipulation. The diet consisted of dried beef myocardium, corn meal, milk, sawdust and, on every other day, fresh meat. Ample water was supplied. The records were made immediately before the dogs were fed. Also, changes in temperature were induced in the room after determining the blood pressure.

In charts 1 and 2 are recorded the continuous dry bulb and wet bulb temperatures of the room, the barometric pressure and the blood pressure as obtained by the mercury manometer described by us. The contents of these charts indicate that there is a marked change in the systolic blood pressure that occurs as a result of sudden changes in the room temperature. There may be other modifying factors that make this relationship more or less intense, such as the barometric pressure

8. Hartmann, F. W.; Bolliger, A., and Doub, H. P.: Am. J. M. Sc. **172**: 487, 1926.

9. A fund was obtained from the Board of Managers of the Presbyterian Hospital to construct this constant temperature room.

and humidity, but it seems that the most important factor is the temperature outside of the body. We believe that fluctuation of blood pressure in dogs of from 20 to 30 mm. of mercury are meaningless in relationship to renal arterial hypertension unless the climatic conditions under which the dogs live are controlled.

A further objection to some of the experimental evidence advanced in regard to the production of arterial hypertension in dogs is the state-

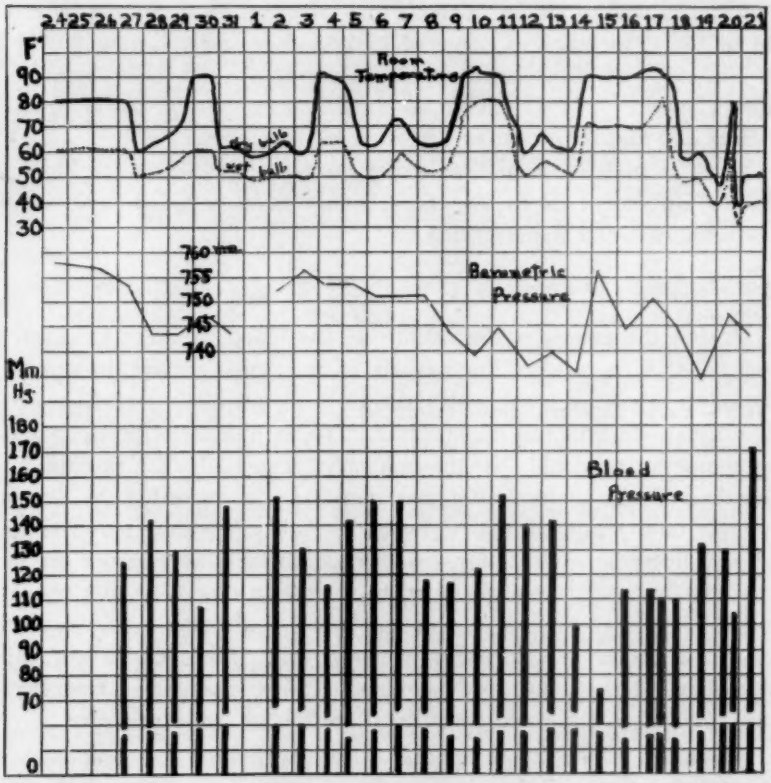

Chart 1.—Alterations in blood pressure due to changes in room temperature. The chart records daily observations that were made in the case of a female dog the average weight of which was 50 pounds (22.7 Kg.). The dog had been in the laboratory for a few months and was accustomed to the necessary manipulations. The two upper transverse lines record the continuous dry bulb and wet bulb temperatures as recorded on a Tycos thermometer. The lower transverse line represents the barometric pressure, which was recorded once a day. The broken vertical lines indicate the blood pressure as determined by the mercury manometer described by us.

ment that the blood pressure of dogs is normally as high as 200 mm. of mercury. We have never observed a dog with a natural arterial

hypertension. It is true that during the first few days of observation, while the dog is frightened and resistant, the systolic pressure is sometimes as high as 175 mm. of mercury, but after the animal becomes accustomed to having observations made, the blood pressure is found to be constant, regardless of weight, sex or age, provided the outside temperature remains fairly constant.

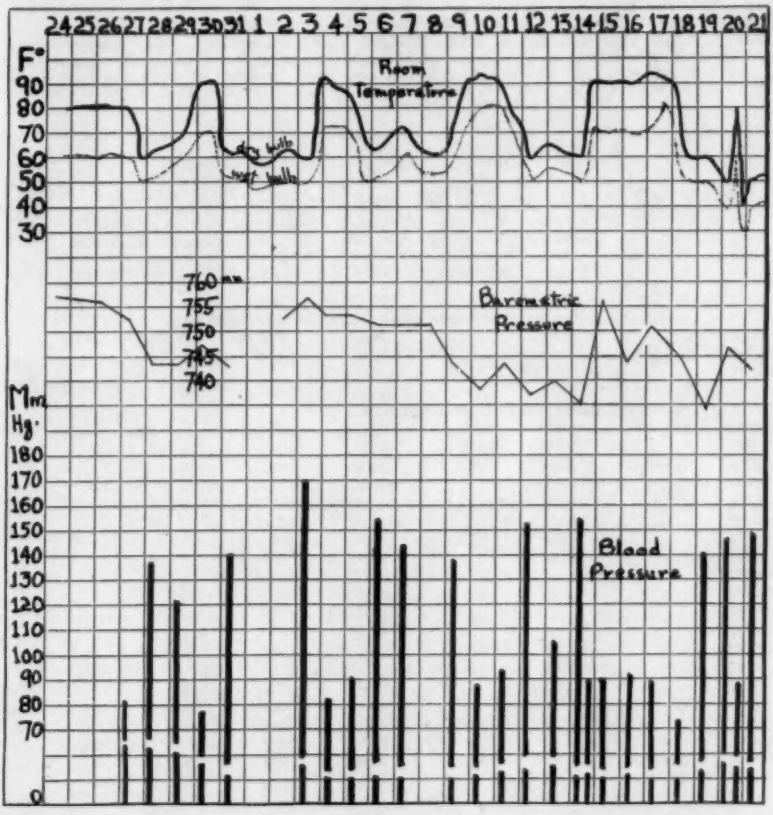

Chart 2.—Alteration in blood pressure due to changes in room temperature. The chart records daily observations that were made in the case of a male dog the average weight of which was 45 pounds (20.4 Kg.). This dog had been in the laboratory for several months and had been used for no experimental work except as a control for the living conditions under which the dogs with renal insufficiency were kept. For further explanation of the chart, see the legend for chart 1.

Still another factor that may be confusing is that a dog must be placed under observation almost daily. If long periods ensue between manipulations, the animal may again, as at first, suffer from fright, and an elevation of systolic pressure may result.

OBSERVATIONS ON BLOOD PRESSURE IN DOGS WITH EXPERIMENTAL RENAL INSUFFICIENCY

During a period of three years, in which seventy-seven female dogs were studied, no rise of systolic blood pressure was observed as a result of renal insufficiency. From this group of seventy-seven animals, we

TABLE 1.—*Protocol of a Dog with Pure Renal Insufficiency*

The results recorded in this table were obtained during the period extending from Aug. 17, 1926, to Nov. 17, 1927. The dog was a female mongrel about 2 years old. The determinations of blood pressure began late in the course of the renal insufficiency, because the apparatus had not yet been devised. As we have found that the blood pressure of dogs averages from 120 to 130 mm. of mercury, we believe it is not assuming too much if that average is adopted for the probable preoperative blood pressure of this dog

Date	Weight, Lb. (Kg.)	Specific Gravity of Urine	Phenol-sulphon-phthalein Excretion, per Cent per Hour	Urea Nitrogen, Mg. per 100 Cc. of Blood	Nonprotein Nitrogen, Mg. per 100 Cc. of Blood	Carbon Dioxide-Combining Power of Blood Plasma, per Cent by Volume	Blood Pressure, Mm. of Mercury	Hemo-globin, Gm. per 100 Cc. of Blood
8/17/26	33 (15)	1.018	....	20.2	38.4	51	...	15.6
8/17/26	Charcoal injected into both kidneys through the renal arteries							
8/19/26	.....	1.006	....	26.6	40.4	..	...	....
8/23/26	30 (13.6)	1.010	....	70.9	102.6	..	...	....
8/26/26	.....	.....	....	.....	.....	..	...	15.0
9/ 9/26	27 (12.22)	1.018	61.0	22.4	43.0	46	...	....
10/ 7/26	Charcoal reinjected into right renal artery							
10/12/26	24 (10.9)	1.009	....	74.0	96.4	..	...	....
10/16/26	.....	1.010	....	125.8	156.2	..	...	....
11/16/26	22 (10)	1.008	14.0	133.3	198.1	34	...	13.5
11/22/26	.....	1.010	....	83.3	100.5	..	...	....
12/15/26	21 (9.5)	1.008	....	142.5	160.0	..	...	....
12/23/26	.....	1.008	....	149.0	241.5	..	...	....
1/ 3/27	.....	1.006	18.0	126.5	165.5	30	...	....
1/17/27	22 (10)	1.008	....	69.9	91.5	..	...	....
1/19/27	.....	.....	....	114.0	171.8	..	...	....
2/ 7/27	.....	1.008	....	63.5	86.5	..	...	....
2/21/27	.....	.....	....	84.5	105.0	..	...	....
2/26/27	.....	1.006	....	64.5	102.2	..	...	....
3/ 7/27	.....	1.008	....	104.2	118.5	..	...	....
3/17/27	.....	1.008	....	107.5	171.1	..	...	....
4/ 4/27	.....	.....	....	102.0	168.3	31	...	12.5
4/11/27	27 (12.22)	1.010	....	55.5	80.9	41	...	....
5/ 4/27	.....	1.008	21.0	62.5	78.5	33	...	....
6/14/27	.....	.....	....	88.0	101.9	..	110	....
6/27/27	26 (11.8)	1.008	18.0	67.8	96.0	26	118	11.0
7/ 7/27	28 (12.7)	1.006	....	108.1	158.6	28	124	....
7/14/27	.....	1.013	....	76.2	106.0	38	120	....
7/25/27	.....	1.012	26.0	30.8	62.5	..	122	....
7/27/27	Charcoal reinjected into left kidney						116	
8/19/27	.....	1.015	....	61.5	115.5	31	112	....
9/15/27	30 (13.6)	1.012	21.0	63.5	126.6	..	118	....
10/ 7/27	.....	1.016	18.0	71.4	126.0	..	126	12.0
10/18/27	.....	1.010	....	88.9	153.2	28	110	....
10/24/27	26 (11.8)	1.007	....	61.5	107.5	30	108	....
11/ 7/27	22 (10)	1.006	15.0	80.0	138.0	..	110	....
11/10/27	.....	1.005	....	80.0	170.8	24	118	....
11/17/27	24 (10.9)	1.007	....	117.6	221.6	21	114	....

At this time, the dog was inadvertently given 5 Gm. of ammonium chloride by a technician and as a result died in two days with a drop of the carbon dioxide-combining power to 16 per cent.

No edema occurred at any time. The arterial system was free from arteriosclerosis, and the heart was not enlarged. The kidneys together weighed 40 Gm. They resembled the usual contracted form described and illustrated by Miller and Apfelbach.[1]

were able to secure only ten that lived long enough to be regarded as presenting chronic renal insufficiency. Infection and excessive renal insufficiency interfered with the use of the others and curtailed the experiments to an acute stage.

TABLE 2.—*Protocol of a Dog with Pure Renal Insufficiency*

The results recorded in this table were obtained during the period extending from Jan. 5, 1929, to Aug. 19, 1929. The dog was a short-haired black and tan female terrier and weighed 24 pounds (10.9 Kg.)

Date	Weight, Lb. (Kg.)	Specific Gravity of Urine	Phenol-sulphon-phthalein Excretion, per Cent per Hour	Urea Nitrogen, Mg. per 100 Cc. of Blood	Nonprotein Nitrogen, Mg. per 100 Cc. of Blood	Carbon Dioxide-Combining Power of Blood Plasma, per Cent by Volume	Blood Pressure, Mm. of Mercury	Hemo-globin, Gm. per 100 Cc. of Blood
1/ 5/29	24 (10.9)	1.042	64	16.0	28.0	54	138	15.6
1/14/29	.....	1.038	..	.....	.....	..	130	....
1/16/29	.....	.....	..	.....	.....	..	124	....
1/29/29	25 (11.3)	1.048	58	12.6	24.8	50	122	15.2
2/12/29	Right kidney removed							
2/24/29	.....	1.028	..	16.8	30.2	48	126	....
3/ 4/29	22 (10)	1.030	49	22.8	41.6	51	118	14.9
3/27/29	.....	1.032	..	36.4	61.2	36.2	114	15.8
4/ 2/29	One branch of left renal artery ligated							
4/ 3/29	21 (9.5)	1.018	..	.....	.....	....	116	14.8
4/ 5/29	.....	.....	..	12.5	31.8	50.4	...	15.7
4/19/29	Charcoal injected into left kidney through renal artery							
5/ 8/29	19 (8.6)	1.024	27	80.0	106.0	27.7	118	15.2
5/28/29	.....	1.016	..	70.0	134.0	24.9	122	14.7
6/ 3/29	20 (9)	1.004	32	83.4	130.9	30.5	114	13.5
6/10/29	.....	1.006	..	96.0	169.5	25.8	110	12.1
6/17/29	18 (8.2)	1.008	..	115.0	160.2	30.5	104	11.9
7/16/29	.....	1.002	..	135.0	245.5	27.9	90	11.4
8/ 2/29	17 (7.7)	1.004	28	147.0	248.0	24.9	116	12.4
8/ 4/29	.....	.....	..	.....	.....	....	130	....
8/19/29	18 (8.2)	1.006	21	135.1	203.8	22.3	104	16.0
8/19/29	(Repeat)	.....	..	134.0	217.7	16.4	108	....

At this time the dog had become very weak, barely able to walk and slightly stuporous, and it refused to eat or drink. Consequently, the animal was killed by air embolism in order that the tissues might be secured in a fresh state. There was no gross or microscopic evidence of arteriosclerosis. The heart was not enlarged. There was no edema of the extremities or of the serous cavities. The left kidney weighed 15 Gm. The right, of course, was absent. The microscopic changes were those described by Miller and Apfelbach.[1]

The animals were observed for from several days to a few weeks before renal insufficiency was induced. During this period, the systolic blood pressure was determined, and the animal was not operated on until a constant level was reached. The phenolsulphonphthalein excretion was determined, the microscopic characteristics, the specific gravity, the ammonia, total nitrogen and chloride concentrations of the urine were observed, and the level of the nitrogenous end-products in the blood and

the carbon dioxide-combining power of the blood plasma were obtained. In tables 1 to 3, we have recorded the protocols of three dogs. The results listed are those necessary to indicate the degree of renal insufficiency and the usual blood pressure levels in such animals.

TABLE 3.—*Protocol of a Dog with Pure Renal Insufficiency*

The results recorded in this table were obtained during the period extending from July 26, 1929, to Dec. 2, 1929. The dog was a female poodle, weighing 16 pounds (8.6 Kg.)

Date	Weight, Lb. (Kg.)	Specific Gravity of Urine	Phenol-sulphon-phthalein Excretion, per Cent per Hour	Urea Nitrogen, Mg. per 100 Cc. of Blood	Nonprotein Nitrogen, Mg. per 100 Cc. of Blood	Carbon Dioxide-Combining Power of Blood Plasma, per Cent by Volume	Blood Pressure, Mm. of Mercury	Hemoglobin, Gm. per 100 Cc. of Blood
7/26/29	16 (7.3)	1.042	45	23.1	49.1	41	128	17.1
7/27/29	.....	1.048	..	25.2	44.9	43	116	16.0
7/29/29	.....	1.046	..	....	....	..	128	....
8/ 2/29	.....	.....	..	....	....	..	136	....
8/ 3/29	15 (6.8)	1.040	..	....	....	..	128	....
8/ 4/29	.....	.....	..	22.4	41.6	47	122	....
8/ 7/29	Charcoal injected into the right renal artery							
8/11/29	.....	1.038	..	26.0	42.0	41	128	....
8/16/29	Charcoal injected into the left renal artery							
8/26/29	.....	1.024	..	37.0	51.8	49	80	....
9/ 5/29	.....	1.020	32	51.0	96.5	34	104	12.5
9/ 7/29	16 (7.3)	1.018	..	....	....	..	116	....
9/14/29	.....	.....	..	80.6	102.9	40	130	12.0
9/19/29	.....	1.022	..	73.0	92.0	32	116	12.2
9/24/29	....	.....	..	....	....	..	118	....
10/ 2/29	.....	1.026	28	76.8	92.0	38	128	16.0
10/ 8/29	.....	1.030	..	....	....	..	124	....
10/11/29	16 (7.3)	.....	..	....	....	..	120	....
10/16/29	.....	1.034	..	....	....	..	144	....
10/24/29	.....	1.030	..	64.4	91.4	44	128	14.7
10/31/29	14 (6.4)	.....	..	50.0	95.0	39	136	....
11/ 3/29	.....	.....	..	....	....	..	142	....
11/ 9/29	.....	1.025	..	....	....	..	128	....
11/13/29	.....	.....	..	....	....	..	124	....
11/21/29	.....	1.024	..	24.4	40.8	51	136	15.7
11/25/29	.....	.....	..	....	....	..	140	....
11/26/29	Charcoal reinjected into right kidney							
11/29/29	.....	1.018	..	116.8	234.0	38	116	....
12/ 2/29	.....	1.020	..	384.0	500.0	27	110	(Dead)

The right kidney was the site of an acute purulent nephritis as a result of the injection of charcoal. The left kidney weighed only 14 Gm. No enlargement of the heart, edema or gross histologic changes of arteriosclerosis were present.

SUMMARY AND CONCLUSIONS

Glomerulonephritis and nephrosclerosis are interpreted at present as general vascular diseases rather than as primary renal diseases with subsequent vascular changes. Also, only part of the clinical manifestations of these two diseases are interpreted as the result of renal insufficiency.

Pure renal insufficiency can be produced in dogs by injecting charcoal particles into the renal arteries, thereby causing infarcts in the glomeruli. The changes that result in animals with pure renal insufficiency of this kind are retention of nitrogen in the blood, decrease in the ability of the kidney to concentrate and dilute urine, decrease in the carbon dioxide-combining power of the blood plasma and decrease in the specific gravity of the urine. Edema and arterial hypertension do not occur.

In the medical literature there are discrepancies between the results of experimenters who have attempted to study arterial hypertension in relationship to renal insufficiency. Some of this discrepancy is due to the failure to take into account the changes in blood pressure that result from alterations in climatic conditions, and some error has occurred because the instruments used in determining blood pressure have given erroneous results.

With changes in room temperature of from 30 to 40 degrees F., a dog's blood pressure may vary as much as 80 mm. of mercury, the pressure going up in a cold room and dropping when the room becomes warm. In addition, the blood pressure of dogs varies easily from fright, and consequently repeated determinations must be made in order to keep the animals accustomed to the procedure.

When these conditions that alter the blood pressure of dogs are taken into consideration, arterial hypertension does not occur in the presence of marked renal insufficiency.

General Review

SYPHILITIC MYOCARDITIS *

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TABLE OF CONTENTS

At the present time syphilitic myocarditis is frequently discussed. While some authors believe that it is often encountered in syphilis in its later stages, others believe that it is rare. Not only does this disagreement prevail at the bedside, but it is also carried to the autopsy table, and even histologic study of the myocardium leads to different interpretations.

My purpose in this paper is, first, to attempt to give a critical review of the literature of syphilitic myocarditis and to relate whatever facts justify this diagnosis anatomically; second, to report results of a study of the myocardium in cases that showed syphilitic aortitis with involvement of the aortic valve. This paper is confined to myocardial changes in acquired syphilis. It deals with myocardial changes called variously chronic syphilitic myocarditis, fibrous form of syphilitic myocarditis, latent syphilitic myocarditis and active syphilitic myocarditis. For convenience, the term syphilitic myocarditis will be used in this paper and will refer only to the lesions just mentioned. Under this term, gummas of the heart, gummatous myocarditis and changes of the heart due to hereditary syphilis are not included, as these conditions are considered to be different from the lesions included in the term syphilitic myocarditis. The gummatous lesions and changes due to hereditary syphilis will be mentioned only when necessary to give a more complete review and understanding of the main subject.

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CHRONOLOGICAL REVIEW OF THE LITERATURE

The first case described in the literature which might possibly have been a case of syphilitic myocarditis was reported by Lancisius in the year 1718. He mentioned an aneurysm of the heart in a patient who had received treatment with mercury. He discussed briefly a possible relationship of the aneurysm to the treatment with mercury. He gave, of course, no detailed studies of the myocardium. But this case is referred to by later writers as possibly a case of syphilitic myocarditis.

Ricord in 1845 is credited with having been the first to describe gumma of the heart. He also described a hemorrhagic infiltration of the myocardium extending over the entire cardiac wall. But because of the facts that the endocardium and the pericardium in this portion were thickened and that the endocardium, in addition, was covered by a thrombus, it is likely that the so-called hemorrhagic infiltration of the myocardium was an infarcted area rather than evidence of myocarditis.

Lebert, who shortly afterward described another case of gumma of the myocardium, made no reference to a possible myocarditis.

Wilks presented before the Pathological Society of London, in 1856, a case of fibroid growth in the ventricular septum of the heart. This has subsequently been referred to as the first case of syphilitic myocarditis. Wilks stated that the growth in the septum looked like a gumma, but he was not convinced that the lesion was syphilitic in origin. He further mentioned that he had seen similar tumors in the muscles and in the tongue and viscera of those who died of inveterate syphilis. In a report on this heart, Baly and Bristowe stated that histologically fibroid nuclei and tuberculous material were found. The muscle fibers were more or less changed. There was fibroid tissue with exceedingly delicate, interlacing fibrils and a meshwork of fibers. Baly and Bristowe remarked, however, that there is no reason to suppose that this case differed in any important particular from other cases that have been brought to the notice of the society as examples of fibroid degeneration of the heart.

Virchow, in 1858, in his paper on the nature of the constitutional syphilitic diseases, mentioned a case (case VII) of gummas of the heart. He pointed out that the myocardium was replaced in patches by a soft, richly vascularized and edematous tissue, found in close vicinity to the gumma. Microscopically, many round cells were found, partially arranged in rows with newly formed connective tissue fibers and, in some places, fatty degenerated cells. Some of the muscle fibers were distinctly atrophic. Virchow raised the question whether or not syphilitic myocarditis exists unaccompanied by the formation of gummas. He concluded that such an occurrence is possible, but neither stated on what basis the diagnosis could be made nor mentioned a case that he himself had seen.

Dittrich in 1852 mentioned a myocarditis (case XI) with an abundance of fibrous tissue in a patient with scars in the liver and spleen and syphilitic scars in the cranium. However, he did not conclude that the myocarditis was syphilitic.

A few years later Virchow, in his "Die krankhaften Geschwuelste" (1864-1865), said that up to a few years ago involvement of the heart in syphilis was regarded as belonging in the realm of fairy tales, but that in the course of the last few years a series of cases of gummas of the heart had been reported. He further stated that, in addition to gummatous myocarditis, fibrous myocarditis occurs in syphilis, but that it is difficult to prove that such cases are syphilitic. He said that in examining the hearts in a large number of cases of syphilis one finds many with multiple fibrous scars in the myocardium, without any demonstrable cause but syphilis. He recommended further research in syphilitic myocarditis.

E. Wagner in 1866 reported a case of syphilitic myocarditis in a stillborn child. His diagnosis was based mainly on the fact that the mother of the child showed signs of secondary syphilis. Histologic examination revealed an increase in connective tissue between the muscle fibers and some fatty degeneration of muscle fibers.

Lanceraux in 1866 differentiated strictly between interstitial syphilitic myocarditis and gummatous myocarditis. Both types of myocarditis are often combined. Grossly, there are white and yellowish areas of connective tissue throughout the heart. Histologically, many cellular elements are present, with a richly vascularized connective tissue.

Aufrecht in 1866 and Mueller in 1868 described the cases of syphilis of the heart in which autopsies were performed at the Pathological Institute of Berlin during the years from 1863 to 1868. Aufrecht mentioned 4 cases of fibrous myocarditis, 1 of which also showed gummatous myocarditis. Mueller recorded 4 cases of interstitial fibrous myocarditis. He stated that the myocardial lesions were syphilitic in origin: first, because no other etiologic factor could be demonstrated to explain the lesions; second, because such types of myocarditis often coincide with gummatous myocarditis, and, third, because there was a similarity between the changes in the myocardium and those found in syphilitic orchitis and syphilitic interstitial hepatitis. Neither author gave histologic details.

Fowler in 1868 described a case of sudden death of a man 45 years old. The heart was enlarged; the lower third of it was occupied by a yellowish-white, semitranslucent material of firm consistency. This material was found in the endocardium and, in some portions, extended through the entire ventricular wall. Histologically, this new material was essentially a fibronucleated structure, having a close resemblance to the ordinary early stage of fibroid degeneration of syphilis. There

was a new formation of connective tissue that seemed to have started from the walls of blood vessels. The coronary arteries, however, were not mentioned.

Morgan in 1872 reported 4 cases, in 3 of which autopsies were performed. One was that of a child, a few months old, who showed gummas in the liver and white spots in the heart. The latter were taken as evidence of syphilis with no other justification but the coincidental finding of gummas in the liver.

Hertz in 1873 described a case of aneurysm of the aorta and syphilitic pneumonia. In the heart a moderate amount of connective tissue between the muscle fibers was seen with lymphocytes and spindle-shaped cells. The belief was expressed that these observations might lead to the conclusion that the patient had had syphilis of the heart.

Baeumler in 1874 stated that in syphilis the heart might show gummas or fibrous myocarditis, sometimes fatty changes and, according to Lanceraux, amyloid degeneration.

Jullien in 1879 stated that he had collected 19 cases of gummas and myocarditis. Gummas and fibrosis of the myocardium sometimes occurred simultaneously. He ventured to say that the occurrence of isolated syphilitic fibrosis of the myocardium is rare, and that if it occurs it is the result of primary diffuse myocarditis. No details were given.

Erhlich in 1880 stated that syphilitic disease of the heart is rare. He described a case of fibrous myocarditis with small grayish-white, necrotic foci, well demarcated, some of which were surrounded by hemorrhagic zones. Histologically, the myocardium showed marked cellular infiltration, many capillaries and some pigment. The muscle fibers close to the necrotic foci were partly atrophic. Many fibers showed no nuclear staining. There was a more or less prominent invasion by pus cells. The necrotic foci were interpreted as areas of coagulation necrosis brought about by endarteritis syphilitica obliterans of the smaller blood vessels. The author believed that such primary changes in the blood vessels may cause secondary syphilitic myocarditis.

Teissier in 1882 reported a case of sudden death in a woman 27 years old. A few vegetations were found on the aortic valve, with fibrous myocarditis and gummas in the myocardium. Histologically, there were diffuse cellular infiltration and perivascular infiltration by round cells; the intima of some of the blood vessels was thickened. The muscle fibers were atrophic.

Chvostek in the same year mentioned a case of fibrous syphilitic myocarditis in the left ventricle, the ventricle being dilated. The walls of the papillary muscles were thickened and, in several places, interspersed with white, dense connective tissue fibers. The myocardium was firm and very pale and had a peculiar fatty shine. Chvostek offered no microscopic description.

Bramwell in 1884 pointed out that in syphilis the arteries adjacent to, or in the midst of, fibroid patches in the heart might be narrowed by endarteritis obliterans.

Paul in 1884 stated that syphilitic lesions may appear in two forms: either as ordinary sclerotic myocarditis accompanied by other syphilitic lesions or as gummy tumors.

Green in 1887 reported a case of aneurysm of the heart with yellowish-white, gummatous-looking material. The posterior coronary artery or a branch of it was involved in this disease and apparently obliterated, but the remainder of the coronary arteries appeared healthy. A clear clinical history of syphilis was specifically mentioned as proof of the syphilitic nature of these changes.

Orth in 1887 stated that the combination of gummas in the heart and fibrous inflammation is commonly encountered. He believed that primary syphilitic fibrosis exists, even though he admitted that it might be secondary to syphilitic endarteritis.

Ashby in 1887 reported a case of sudden death. The heart showed white patches of fibrosis. Microscopically, there were round cells, spindle cells and connective tissue fibers. Some of the arteries were thickened in places. The case was diagnosed as possibly syphilitic myocarditis.

Ziegler in 1887 stated that gummas of the heart are rare; that fibrous myocarditis is found somewhat more frequently, as a result of hereditary or acquired syphilis, and that some of the cases reported in the literature as cases of syphilitic fibrous myocarditis are more likely cases of arteriosclerosis.

Bargum in 1888 reported the case of a 45 year old man. The left ventricle was somewhat hypertrophic; the coronary vessels were normal. In the wall of the left ventricle several fibrous spots were noted, which were stellate. Microscopically, the fibrous spots showed much connective tissue, a few cells and many blood vessels. The arteries were the seat of perivasculitis. The muscle fibers were atrophic. Small nodular areas of round cells with necrosis also were demonstrable. The author believed that this was a case of gummas of the myocardium combined with syphilitic myocarditis.

Mauriac in 1889 stated that the heart is the rarest location of syphilis. From 25 to 30 such cases were known. He stated that if gummas are absent, it is difficult to differentiate syphilitic sclerosis of the heart from other types of sclerosis. The vascular changes found in such cases consist mainly of periarteritis, with the predominating changes in the adventitia. The intima usually is also infiltrated, and the lumen, in some instances, is completely obliterated.

Buchwald in 1889 remarked that syphilitic myocarditis is a frequent finding. He held that the changes are characteristic pathologico-

anatomically. The characteristic features, however, were not mentioned. He concluded that a large number of persons afflicted with syphilis sooner or later show syphilitic myocarditis with or without diseased blood vessels.

T. Lang, who in 1889 had observed 44 cases of syphilis of the heart, stated that syphilitic myocarditis always is fibrous or gummatous. In his "Vorlesungen ueber Pathologie und Therapie der venerischen Erkrankungen," he further stated that the diagnosis of syphilis in cases of chronic myocarditis must be supported by the anamnesis and the presence of other manifestations of syphilis. He did not give histologic details.

Schwalbe in 1890 mentioned that syphilitic interstitial myocarditis is a disease per se and occurs independent of the presence of gummas or infarcts. He did not refer, however, to his own observations.

Saccharyin in 1890 stated that the basis for the diagnosis of syphilis of the heart lies in the history of the case and the simultaneous finding of syphilis in other internal organs.

Bogosslowsky in 1891 mentioned 2 cases of syphilitic myocarditis in which the diagnosis of syphilis was based on the observation that the condition of the patients improved after the administration of potassium iodide.

Cohnheim, in 1891, in describing a case of gumma in the intraventricular septum, did not mention syphilitic myocarditis. Juergens in 1891 mentioned a case of cardiac gumma among 4 cases of so-called primary tumors of the heart, but made no reference to myocarditis.

Stockton in 1891 stated that in a patient who had syphilis, and who was intolerant to mercury, endocarditis and nephritis had developed. He did not mention the myocardium nor give a detailed description of the heart.

Mracek in 1892 stated that syphilis of the heart is rare. He divided the changes of the heart brought about by syphilis into two groups. To the first group he assigned the direct products of syphilis, namely, the gumma and a specific inflammation which, according to its end-stage, is called fibrous sclerosing myocarditis, and to the second, changes occurring secondarily to lesions of the first group, i. e., atrophy of muscle fibers, regressive changes brought about by vascular lesions, fibrosis and aneurysms. The histologic criteria of syphilitic myocarditis are old fibrous tissue in addition to newly formed connective tissue and granulation tissue. The portions of the myocardium that are situated close to the branches of the coronary vessels or close to the vasa vasorum are involved first. Among the 3 cases which the author reported was a case showing fibrous myocarditis with vascular changes and necrosis.

Palma in 1892 described a case of so-called syphilitic myocarditis. A portion of the descending branch of the left coronary artery was obliterated. The myocardium showed granulation tissue also in portions

that were supplied by branches of the coronary artery that were not completely obliterated. There was an abundance of connective tissue, but no calcification. This case also showed gummatous orchitis. Sections of the coronary revealed nothing indicative of syphilis. It seems unwarranted to speak of syphilis of the coronary artery or of the myocardium in this case merely because a gummatous orchitis was found coincidentally.

Rolleston in 1893 found in the heart of a 34 year old man who died suddenly many pea-sized nodules that consisted histologically of round cell infiltrations. Weight is put on the fact that old syphilitic changes were found in the testis.

Mracek in 1893 reviewed the literature on syphilis of the heart. He had collected from the literature reports of 9 cases of fibrous myocarditis, 8 of fibrous and gummatous myocarditis and 15 of myocarditis combined with pericarditis or endocarditis. In addition, he reported a case of chronic fibrous myocarditis with obliterating endarteritis and necrosis of the myocardium. He emphasized the fact that the diagnosis of syphilis can be made only through analogous syphilitic changes in other organs.

Pearse in 1893 described clinical observations in a case of angina pectoris. No postmortem observations were given.

Kockel in 1893 reported 2 cases. The first showed fibrous myocarditis with partial aneurysm of the heart and a small gumma. Histologically there was an increase in connective tissue which was poor in nuclei, but which showed in a few places a small, circumscribed cellular infiltration. Several newly formed capillaries were also noted. The smaller arteries showed inconstant intimal thickenings, in not a few instances so advanced as to lead to marked narrowing of their lumina. He ventured the opinion that the myocarditis was a syphilitic inflammation, the result of an obliterating endarteritis. The second case occurred in a man, aged 19, who showed a circumscribed nodule on the intima of the descending branch of the right coronary artery, which was thrombosed in this region. The heart showed many white spots. The nodule consisted histologically of accumulations of triangular and spindle-shaped nuclei, with a few round cells. There was some necrosis in the center. Syphilis as the causative agent seemed probable, because of the youth of the patient and because of the fact that only one nodule was found. There was no other manifestation of syphilis, however. There is no detailed histologic description of the heart.

Barlaro in 1893 reported 2 cases of syphilis of the heart, both of which showed angina pectoris clinically. In one case a gumma of the heart was combined with fibrous myocarditis.

Birsch-Hirschfeld in 1894 attributed a diffuse, chronic myocarditis, among other agents, to syphilis. He classified syphilis of the myo-

cardium into gumma and diffuse myocarditis. Gummatous foci may lead to the formation of an aneurysm and rupture of the heart.

Hektoen in 1894 reported the case of a 6 weeks old child. The myocardium showed many whitish, round areas, measuring up to 1 cm. in diameter, which were of a homogeneous surface and which showed no calcification. Histologically, there was an infiltration of round and oval nucleated cells around smaller vessels. The larger subepicardial vessels were not involved. There was no proliferation of endothelial cells. The adventitia contained more connective tissue fibers. The interstitial changes were so marked as to lead to the gross diagnosis of gummas.

Loomis in 1895 classified the syphilitic lesions of the heart into four groups, namely, gummas, fibroid induration, amyloidosis and endarteritis obliterans, often producing infarcts. He stated that, besides the formation of gummatous tumors, syphilis gives rise to an indurated myocarditis, a lesion that in its later stage is hardly distinguishable from fibroid disease due to other causes. It is possible to arrive at the origin of these new growths only by inference from the history of the patient, and from the presence of constitutional syphilis, especially gummatous tumors in other situations. It seems probable, as suggested by Ziegler, that the inflammatory induration as a consequence of congenital or acquired syphilis is much more common than the development of gummas. Loomis assumed that a syphilitic fibrous induration presents localized, well defined fibroid areas situated in the substances of the heart, or diffuse irregular patches of new fibroid tissue with endarteritis obliterans of minute arteries or interstitial myocarditis due to a partial absorption of gummas and replacement by connective tissue. He had seen 15 cases of fibroid myocarditis in which the diagnosis was made by microscopic examination, 3 of which were, beyond all doubt, of syphilitic origin.

Philips in 1896 reported that among 4,000 cases in which autopsies were performed at the Pathological Institute of Kiel, 99 were cases of syphilis and 397 were possibly cases of syphilis. None of these 496 cases showed a syphilitic fibrous process in the heart.

Stolper in 1896 found, among statistical material consisting of 2,995 cases, 61 of acquired syphilis. One case showed a gumma in the heart and another a possible diffuse gummatous infiltration of the heart. He presented the following questions which had not been answered: Does syphilis of the heart produce fibrous productive inflammation, or is the fibrous tissue found in such hearts scar tissue replacing old necrotic areas? What relations are there between the disease of the muscles and the vascular changes? Are the changes caused by syphilis or by something else? Syphilis might have been the cause in 2 of his cases. The myocardium showed a cellular infiltration of the adventitia of the

smaller vessels and some endarteritis obliterans. The author preferred to speak of fibrous myocarditis in syphilitic persons instead of syphilitic myocarditis.

Grassmann in 1897 remarked that the prevalent opinion of the rarity of syphilis should be corrected, and that only gummas of the heart are rare. His paper is purely clinical, but gives a historical review of this subject.

Philipps in 1897 mentioned fibrous myocardial changes in syphilitic patients. He spoke of 25 cases in which there were gummas, syphilitic infiltration or fibrosis, but he gave no histologic data.

Rosenbach in 1897 mentioned among syphilitic conditions of the myocardium, gumma, fibrous inflammation, endarteritis obliterans with infarcts and new formation of connective tissue, but stated that none of these lesions shows enough characteristics to allow a diagnosis of syphilis.

Herrick in 1897 stated that fibrous and gummatous forms of syphilitic myocarditis had been observed. The fibrous form is characterized by grayish areas or streaks in the myocardium, single or multiple. Areas when fully fibrous differ in no respect from fibrous myocardial patches due to coronary obstruction with consequent myomalacia and subsequent fibrous patches. The concomitant gumma is unmistakable evidence of syphilis. Complete exclusion of coronary disease also reveals the syphilitic nature of this form of myocarditis. It is to be remembered that coronary endarteritis obliterans syphilitica may be a cause of myomalacia and fibrous change. Care must be taken lest one too frequently assign a syphilitic origin to fibrous myocarditis, especially because of the fact that Orth stated that fibrous myocarditis is clearly recognized as syphilitic only when gummas are also present.

Adler in 1898 demonstrated 2 cases of Addison's disease brought about by gummas of the suprarenal glands. One of these cases revealed an interstitial myocarditis. There was a mere cellular infiltration with some coagulation necrosis. No endarteritis or periarteritis was demonstrable. The heart in the second case also showed evidence of periarteritis and endarteritis of the coronary arteries, as well as some hemorrhage.

LeCount in 1898 reported gummas in the heart in a case of congenital syphilis. There were white areas, circular in form, in the myocardium. Histologically, a marked infiltration by round or fibrillated cells was found most marked around the arterioles. Multiple foci of interstitial myocarditis were present, with polymorphonuclear leukocytes and also areas of degeneration and necrosis. The title "gummata," the author stated, is a matter of preference.

E. Lang in 1899 remarked that there is a simple fibrous syphilitic myocarditis with multiple fibrous cicatrices in the cardiac muscle. In

such cases partial aneurysms have been repeatedly observed. He did not give the histologic features by means of which such a myocarditis might be recognized.

Rosenthal in 1900 pointed out that the first state of syphilitic myocarditis is a specific endarteritis, while the end-stage is a fibrous scar. He differentiated a gummatous form and an interstitial or fibrous form. In the description of a clinical case of syphilitic myocarditis, he reached the conclusion that in syphilis myocarditis may develop on the basis of functional overactivity of the heart.

Grassmann in 1900 and 1901, in papers dealing with clinical aspects, reached the conclusion that in early syphilis the heart is frequently involved.

Stevens in 1901 stated that syphilis of the myocardium manifests itself as a more or less fibroid induration, as a gummatous growth or, rarely, as amyloid degeneration. Fibroid induration or interstitial myocarditis is usually secondary to syphilitic endarteritis. But the myocarditis also can result from the direct action of the specific poison on the muscle cells or on their sheaths, since a few cases have been noted in which no lesion of the coronary arteries could be detected.

Krehl in 1901 pointed out that syphilis of the heart is not rare. All parts of the heart may be involved. Syphilitic myocarditis may be the result of vascular changes, may be present in the form of gummas or may manifest itself as a diffuse interstitial inflammation.

Wagner and Qwiatkowski in 1903 reported a case of syphilis of the heart. Grossly, dry and yellowish-gray areas were found in the myocardium. Histologically, spindle-shaped cells and necrotic portions were demonstrated. Evidence of endarteritis was shown. There was much fibrous tissue in the midst of the muscle tissue.

Quensel in 1903 stated that the fibrous myocarditis found in the heart in cases of syphilis offers nothing characteristic of syphilis, either grossly or histologically. A diagnosis of syphilitic myocarditis is a diagnosis based on probability only. In a study of 121 cases of syphilis he found fibrous myocarditis eight times in patients who were older than 40 years, and five times in patients younger than 40. But he was not certain that syphilis was the underlying cause of the myocarditis.

Busse in 1903 reported a case of syphilitic inflammation of the heart and of the external muscles of the eye. The heart showed a recent inflammation and scar tissue. Many endothelial cells and giant cells were present. There was an intimal proliferation of the smaller arteries. The muscle fibers were the seat of a fatty metamorphosis, but no necrosis was demonstrable. A search for tubercle bacilli gave negative results. In the author's opinion the peculiar mixture of scar tissue and

recent inflammation combined with the presence of giant cells is characteristic of syphilis. It is probable that this case presented gummatous myocarditis.

Cowan in 1903 showed a picture (fig. 11) of the heart in a case of syphilis in the secondary stage. The lumina of the arteries were but little interfered with. There was newly formed connective tissue, which was much vascularized and which extended between the individual muscle fibers. He stated that some scars of the myocardium may be the result of gummas.

Romanow in 1904 reported a case of productive myocarditis which was thought to be syphilitic in origin. He stated that syphilis of the heart is not too rare.

Stockmann in 1904 reviewed 76 reports of cases which he had collected from the literature and reported 4 cases which he had observed. Many of these cases showed myocardial fibrosis in addition to gummas.

Adler in 1904 stated that primary interstitial myocarditis may occur very early in syphilis. There is cellular infiltration in the adventitia of the small arterioles. From these proliferations as starting points, strands of cellular infiltration transverse the adjacent myocardium. The muscle fibers, which first are normal, degenerate gradually, while others become atrophic. The media of the arteries become fibrous, the intima proliferates and an obliteration of the arterioles results. An extreme fibrous degeneration of the cardiac muscle takes place. Cardiac syphilis is not rare; on the contrary, it is rather a common disease.

Renvers in 1904 found among 2,000 cases of cardiac disease 26 which were anatomically cases of syphilis of the heart, 3 of which showed gummas. He did not give a histologic description of these cases.

Huchard in 1905 stated (page 885) that paralysis of the heart may be caused by chronic syphilitic myocarditis. He did not give any histolcgic details.

Takeya in 1906 described a case of gummatous pericarditis and a case of gummas in the myocardium. But he did not mention syphilitic myocarditis.

Stoeltzner in 1906 reported a case of syphilitic myocarditis in a child 2 years old. There were white and yellow spots in the myocardium, which were connected with one another Histologically, young granulation tissue was found. No giant cells or necrotic portions could be demonstrated. The patient had had lobar pneumonia six weeks previously. This case, even though reported as a case of syphilitic myocarditis, showed nothing characteristic of syphilis.

Buschke and Fischer in 1906 found in a case of congenital syphilis in a child 3 weeks old an interstitial diffuse myocarditis. There was

a marked increase of cellular connective tissue, which was edematous. A few circumscribed infiltrations with central necrosis and destruction of muscle fibers were noted. Infiltrations by lymphocytes were found surrounding smaller branches of the coronary arteries. Many spirochetes could be demonstrated by the use of the Levaditi method. They were found around the infiltrated vessels and within their lumina.

Janeway and Waite in 1907 reported a case of gummas of the heart and liver. There were many eosinophils in the myocardium in addition to the gummas.

Herxheimer in 1907 pointed out that an infiltration by round cells along the blood vessels of the interstitial tissue is characteristic of syphilitic fibrous myocarditis. The muscle fibers suffer secondarily by pressure and as a result of vascular disturbances. Scar tissue is found mainly in the left ventricle, close to the apex. Gummatous myocarditis is often combined with fibrous myocarditis.

Pitzner in 1908 reported 7 cases of syphilis in which fibrous myocarditis was found. The author believed that the localization of the fibrosis in the heart, namely, in the region of the interventricular septum, is characteristic of syphilis. He also mentioned that in these cases sclerosis of the coronary vessels was often missing. Thorel, however, in discussing the changes, stated the belief that all of them could be explained on a nonsyphilitic basis.

Landois in 1908 reported 3 cases of syphilis of the heart. The first case was that of a 9 year old girl afflicted with congenital syphilis. The heart showed several gummas. In the second case, which occurred in a 46 year old man, the heart showed white scars throughout the myocardium. Histologically, connective tissue was present in these areas, with only a few nuclei. Cells were found surrounding small vessels, the lumina of which were obliterated. The author believed that the diagnosis of syphilis of the heart was justified because the larger branches of the coronaries showed no arteriosclerotic changes, while the small branches were partly obliterated. (It might be stated that the patient had died of diphtheritic enteritis.) In the third case, which occurred in a 56 year old woman, the heart was the seat of many gray, scarlike foci. The intima of the coronary arteries was smooth. Histologically, many round cells and scar tissue were found between the muscle fibers. The author stated that the inflammatory reaction as such is not characteristic of syphilis. He mentioned, however, that there is no other disease known which produces such an outspoken fresh interstitial inflammation involving the entire cardiac muscle and later appears only in certain foci.

Adami and Nicholls in 1909 stated that syphilis is an infrequent cardiac disease. It may lead to gummatous foci, to fibroid induration, to amyloid infiltration and to endarteritis obliterans, often causing

infarction. The indurative inflammation is perhaps the most common. The authors did not state the histologic criteria of these syphilitic conditions.

Romberg in 1909 remarked that, more frequently than gumma, diffuse interstitial myocarditis is found in the heart in cases of syphilis.

Powell in 1909 stated that syphilitic myocarditis invariably occurs either immediately adjacent to gummas or secondary to, and in the territory of, specific arteritis. Syphilis may affect the myocardium in the form of syphilitic arteritis with secondary necrosis and ultimate fibrosis, in the form of gummas or in the form of a diffuse chronic myocarditis of specific nature affecting a considerable portion of the heart. It is, however, doubtful whether this form does not originate in the fusion of scattered gummatous depositions. He further stated that knowledge of syphilitic myocarditis is mainly derived from post-mortem observations in cases in which by no means all of the patients died with cardiac symptoms.

Berblinger in 1910 described a case of what he called gummatous myocarditis. Histologically, many round cells were found, partly diffuse, partly localized. There were many fibroblasts present, but no well defined nodules consisting of endothelial cells. There was a marked vascularization of the granulation tissue. Some sections showed many connective tissue fibers which were rich in nuclei, while others revealed old fibrous connective tissue without nuclei. A few fields showed perivascular infiltration. There was no caseation.

Warthin in 1911 maintained that a special form of myocarditis exists which is due to the presence of spirochetes resulting from congenital syphilis. In cases of this condition, grossly, light-colored patches were found in the myocardium. Histologically they consisted of fibroblastic and myxomatous tissue with lymphocytes and large endothelial cells. Obliterating endarteritis was not uncommon. There were foci of small cell infiltration. The presence of the spirochetes was demonstrated by the Levaditi stain.

Billings in 1911 stated that in syphilis an obliterating endarteritis might especially involve the coronary arteries. Such a condition of the coronary arteries frequently results in fibrous myocarditis and the development of cardiac inadequacy and anginal attacks in the young. Sudden death may supervene.

Warthin in 1912 stated that in syphilitic hearts focal or diffuse areas of fatty degeneration of the myocardium may be associated with the presence of numerous spirochetes, without reaction on the part of the interstitial tissue. Such changes probably represent "a very acute or mild (latent) infection." They occur frequently in congenital syphilis. Calcification or fibroid changes may follow the parenchymatous changes, without a definite interstitial inflammatory reaction. In

such cases the spirochetes are few or have entirely disappeared, according to the stage of the secondary process. Warthin mentioned that focal areas of fatty degeneration of the myocardium also occur in other infectious diseases.

Benda in 1913 remarked that the seat of syphilitic changes in the heart is the myocardium. The changes may appear in the form of diffuse syphilitic inflammation, of fibrous inflammation or of gummatous inflammation and granulation tissue. In the discussion of Benda's paper, it was brought out that every author had confessed that he was unable to find specific signs of syphilitic myocarditis. Other diseases might cause similar changes in the myocardium. Fibrosis following gumma has nothing to do with syphilitic myocarditis.

Heller in 1913 could not decide whether the changes found in the hearts of 35 syphilitic patients were syphilitic. He was inclined to believe, however, that they were syphilitic in origin.

Brooks in 1913 reported that in 44 of 50 cases of syphilis there was a diseased myocardium. True gummas were found in 5 instances. The inflammatory process in the myocardium consisted of round cell infiltrations around the arterioles or of foci of fibrosis. The probable sequelae of such changes are cardiac aneurysms, which were present in 3 cases. A disease of the coronary arteries was found in 35 cases; the changes were of a relatively greater degree than the general arterial changes. In 5 cases in which the changes were pronounced, the age of the patients was below 30 and in 4 others below 40. Brooks maintained that cardiac involvement might develop early in syphilis.

Braun in 1913 mentioned that involvement of the myocardium might occur early in syphilis. The diagnosis, however, is based almost entirely on the anamnesis. In the late stages the heart may show syphilitic myocarditis leading to chronic myocardial insufficiency clinically. The author did not mention any cases of his own, but reviewed some reports in the literature on this subject. He pointed to the fact that in the textbooks of Bamberger, Zetelmayer, Friedreich and von Duck no mention is made of syphilitic myocarditis.

Sachs in 1913, reviewing the literature on this subject, remarked that some of the investigators were of the opinion that syphilis is the most important factor in the production of heart disease.

Rosenfeld in 1914 described a case in which scars were found in the papillary muscles of the heart. There was, besides, syphilitic aortitis with encroachment into the mouth of the left coronary artery and with almost complete obliteration of the mouth of the right coronary artery. The author concluded that pathologically syphilitic fibrous myocarditis cannot be distinguished from the usual fibrous (nonsyphilitic) myocarditis.

In 1914, Warthin, in one paper, reported 41 cases of active syphilis in 36 of which active lesions in the heart were found. He stated that syphilis was determined either by the presence of spirochetes or by the characteristic lesions of the tissues. He stated that in the latter the spirochetes were being demonstrated as fast as the work could be carried out. Warthin's other paper of 1914 will be referred to later.

Saltykow in 1914 reported a case of specific productive myocarditis. He described pale yellow areas in the myocardium. Histologically, granulation tissue was found, with many giant cells. There were necrotic portions, a few round cells and many endothelial cells. No tubercle bacilli and no spirochetes were found. The author was not certain that this was a case of syphilis.

Cabot in 1914 classified 600 recent cases in a hospital. Thirty-two of the patients showed failing hearts. These hearts showed partial valvular lesions. There was no evidence of nephritis or of arteriosclerosis, nor had any history of rheumatism been obtainable. But all these patients had given a positive Wassermann reaction. The author stated that the permeation of the myocardium of the congenitally syphilitic person with spirochetes makes it probable that in adults many cases of myocarditis are due to syphilis.

Brooks and Carroll in 1914 maintained that the heart may be affected in early syphilis. These authors, however, did not base their evidence on postmortem studies, but on clinical evidence.

Cesa Bianchi in 1914 described the case of a man, aged 39, who gave a history of syphilis of fifteen years' duration and a history of a rheumatic infection of two years' duration. The myocardium in the upper portion of the left ventricle showed a gelatin-like, grayish-white region, which on section showed new formation of connective tissue and of blood vessels, edema and perivascular infiltration by small cells. The periphery of this area showed giant cells and many plasma cells. There was no caseation or necrosis. The author spoke of granulomas. There was endarteritis of the small arteries. The finding of spirochetes was reported. The original article, however, shows no picture of the spirochetes. It seems likely that this case should be classified as one of gumma, rather than as one of syphilitic myocarditis.

Anders in 1915 remarked that involvement of the myocardium is not infrequent in the course of syphilis. While endarteritis is a frequent important lesion, actual gummas of the myocardium are distinctly infrequent. The author stated that, while he would not go so far as to say, along with some recent investigators, that syphilis is the principal factor in the production of heart disease, it can at least be safely assumed that rheumatism and syphilis head the list as causes of organic injury to this organ. He further stated that it is definitely known that the spirochete of syphilis has a selective action on the heart. But

neither the cause of the selective action nor the source of the information is revealed in this article.

Allbutt in 1915 remarked that the combination of syphilis of the heart and syphilis of the aorta is somewhat infrequent.

Thorel in 1915 maintained that, contrary to clinical observations, pathologico-anatomic experience teaches that cases of myocardial syphilis are extremely rare.

Citron in 1916 stressed the point that spirochetes are found in the heart in cases of congenital syphilis, but that disease of the heart is rare. Whether fibrous myocarditis results from localization of spirochetes in the interstitial tissue is not certain. This surely is, at least, not an everyday finding.

Symmers in 1916 reported anatomic lesions of syphilis in 314 of 4,880 cases in which autopsies were performed. Syphilitic aortitis was reported found in 175 cases, but changes in the myocardium were not mentioned.

Warthin in 1916 found active syphilitic lesions and spirochetes in the heart in 36 of 41 cases of syphilis. He did not mention the criteria of syphilis of the myocardium.

Hirschfelder in 1918 mentioned syphilitic fibrous myocarditis, without giving details.

Moore in 1918, in a clinical paper, ventured the opinion that cardiac lesions occur earlier in syphilis than has been thought. The cardiac lesions are most frequently present in the form of myocarditis. He did not say how he reached this conclusion.

Warthin's article of 1918 will be referred to later.

Aschoff in 1919 spoke of diffuse interstitial myocarditis with the formation of giant cells. He did not discuss any other form of syphilitic myocarditis.

Pilz in 1920 reported a case of constriction of the mouths of the coronary arteries in syphilis, resulting in necrosis, infarction and final rupture of the heart. He did not mention syphilitic lesions of the myocardium.

Sternberg in 1920 said that syphilitic arteritis of the coronary arteries may lead to circumscribed myomalacia, with the formation of scar tissue and possible rupture of the heart. He did not mention syphilis of the myocardium.

Takata in 1920 described 4 cases of gummas in the myocardium and 1 case of possibly syphilitic myocarditis. This case showed small, circumscribed cellular infiltrations close to the smallest blood vessels, mainly of round cells and plasma cells. There was new formation of connective tissue. Pigment was present in polymorphonuclear leukocytes. Some of the smaller arterioles and venules showed thickened

intima, while the larger arteries appeared normal. The veins showed circumscribed infiltrations by plasma cells; none were found in the arterioles.

Cowan and Rennie in 1921 discussed syphilitic aortitis and syphilitic aortic incompetence. In 3 of their cases the lumen of the left coronary artery was thrombosed. These cases showed myocardial infarctions. The authors presented 4 cases in more detail. None of them gave evidence of syphilitic myocarditis.

Chapman in 1920 maintained that in any case of organic heart failure in which the history of a more usual infection is not obtainable syphilis should be considered the causative agent. This is entirely a clinical paper, not confirmed by observations at autopsies.

Lemann and Mattes in 1920 reported an investigation carried out on 55 bodies showing syphilitic aortitis. Forty-one hearts were normal, on gross inspection, and 16 of these proved, on histologic examination, to be free from changes. Seven hearts showed scars in the myocardium, 5 offered areas of softening, 4 were the seat of fresh pericarditis (2 of these were from bodies that showed pneumonia), and in 1 heart an old pericarditis was demonstrable. Localized and diffuse areas of fibrosis were found in 14 hearts, whereas lymphocytic infiltration was present in 24. In 2 hearts spirochetes were found. One of these hearts showed no other abnormalities. Fatty degeneration of the cardiac muscle was found in 11 hearts; necrosis of the muscles, in 2. Subepicardial collections of lymphoid cells were demonstrable in 2, brown atrophy in 5 and simple atrophy in 3 hearts. Atrophy, necrosis and hemorrhage were found in 1. One heart was the seat of a microscopic abscess (the case showed other signs of clinical sepsis, but no other observations at autopsy were revealed). Two hearts showed gummas microscopically. The authors did not intend to suggest that all of these various changes in the cardiac muscle were due to syphilis. Certain changes, however, were suggestive. Scars and areas of softening, central necrosis of muscle tissue with connective tissue infiltration and beginning vascularization at the periphery of the lesion and lymphoid infiltration in the areas of vascularization were often observed. The end-picture of some of the lesions, namely, scarring with connective tissue replacement and diffuse infiltration by lymphoid cells, would make one suspicious of a healed gumma.

Macfie and Ingram in 1921 reported 3 cases occurring in boys from 6 to 12 years old. There was a rupture of the heart in 2 cases, and an old aneurysm in 1 case. The heart in 1 case showed a gumma-like structure; the other 2 cases offered a slight endarteritis of the coronary arteries, which possibly might be of syphilitic origin.

Spalding and von Glahn in 1921 reported a case of syphilitic rupture of the papillary muscle of the heart. Microscopically there were areas of necrosis surrounded by leukocytes. Some of the muscle fibers contained fat droplets. The Levaditi stain showed a moderate number of spirochetes. The spirochetes reproduced in the illustration of this article are not typical spirochetes. The histologic changes differed from those in a gumma, no plasma cells being present. The outlines of the preexisting tissue in the areas of coagulative necrosis were completely obliterated.

Brooks in 1921 stated that syphilis in the early and later stages involves the heart with great frequency. Syphilis may involve the pericardium, myocardium and endocardium and the conus arteriosus. Any form of syphilitic lesion, with the exception of the chancre, may be found in the heart. He believed that there are many cases of syphilis that show no anatomic evidence of cardiac involvement, notwithstanding that the heart is probably one of the most frequently involved viscera. The author gave the following data, without going into the microscopic details or even discussing differential diagnostic features: Among 50 cases, 35 showed coronary arteritis of a relatively greater degree than that found throughout other blood vessels. Because only one circumscribed area of the coronary artery might be involved, such an area might easily be overlooked by investigators. In 5 hearts gummas were found, usually of relatively small size. Syphilitic cardiac fibrosis originating from gummas was present in 4 cases. In 5 cases fibrosis and fatty degeneration and infiltration could be demonstrated. Syphilitic myocarditis was found in 6 cases (but no criteria for this diagnosis were given). In 3 of these cases there were cardiac aneurysms. The essential lesion leading to the aneurysmal formations was thought to be a coronary endarteritis.

Reid in 1922 stated that involvement of the heart may begin before or during the so-called secondary stage of syphilis. The infection of the heart and aorta by the spirochetes of syphilis produces one of the most important types of heart disease. In recent years there has been an appreciation of the fact that coincident with the syphilitic lesion of the aorta, the heart proper is usually involved. He further mentioned that sclerosis of the larger branches of the coronary arteries is rare in syphilis.

Borst in 1922 mentioned the occurrence of syphilitic scars in the myocardium. He stated that an aneurysm of the heart brought about by coronary sclerosis or thrombosis rarely leads to rupture of the heart, contrary to the aneurysm that is found as a result of syphilitic scars of the myocardium.

Wiltshire in 1922 made a statement in regard to diffuse interstitial syphilitic myocarditis as follows: "This is seen when the process has

been generally distributed about many of the small branches of the coronary artery. A diffuse fibrosis also is produced when the whole heart wall has been relatively starved over a considerable period by lesions causing narrowing of the openings or main trunks of the coronary arteries." The author did not cite any case of his own in which an autopsy had been performed, nor did he give a detailed histologic discussion.

Kaufmann in 1922 stated that not all cases of fibrous myocarditis in syphilis can be explained on the basis of vascular changes, but that cases are found in which toxic degeneration of the muscle fibers has occurred primarily and the proliferation of connective tissue secondarily. On the other hand, primary interstitial fibrous myocarditis has occurred in syphilis, although it is not characteristic.

Fraenkel in 1923 stated that there is no anatomic material proving the occurrence of syphilitic heart disease in the secondary stage of syphilis. As concerns the last stage of syphilis, the author differentiated between gummas of the heart and interstitial myocarditis. He stressed the point that the latter has no characteristic features.

Reid in 1923 stated that syphilis of the heart and aorta maims and kills those in the prime of life. Of 100 patients of the Boston City Hospital who successively came to autopsy, 7 showed syphilis to be the apparent cause of the changes in the heart and aorta. The author did not give the histologic details. He stated that every case of syphilis is a case of potential heart disease.

Levine, in discussing Reid's paper, asked those present at the meeting the following question: "What is the consensus of opinion as to the occurrence of syphilitic myocarditis without other vascular changes due to syphilis?" No one had any definite opinion as to the frequency of such occurrence, but the general feeling was that uncomplicated syphilitic myocarditis is rare.

Bloch in 1923 differentiated between acute syphilitic myocarditis, which is a true inflammation of the myocardium, and subacute myocarditis, which consists of a perivascular infiltration of embryonal cells, and which reveals an abundance of connective tissue and sometimes gummas. He stated that there is no pathologist who is able to make the diagnosis of syphilis with certainty ("d'une coupe"). The histologic examination cannot confirm the syphilitic nature of the lesion (quoting Nicolas and Moutot). Only the finding of spirochetes assures one that the lesion in question is syphilitic.

Wittgenstein and Brodnitz in 1924 stated that of 1,686 patients with cardiac and circulatory diseases, 542 were syphilitic. In 29 cases the diagnosis was inadequacy of the cardiac muscle, myodegeneratio cordis, myocarditis or gummas of the myocardium. The diagnoses were based entirely on clinical findings. No case in which autopsy was performed was included in this report.

Von Glahn and Wilshusen in 1924 reported 2 cases of syphilitic aortitis combined with rheumatic myocarditis.

Scott in 1924 mentioned that among 25 patients showing syphilitic aortitis with involvement of the aortic valve post mortem, 8 showed the combination of fibrosis, cellular infiltration and mucoid degeneration, comparable to the histologic picture of syphilitic myocarditis described by Warthin. Cicatricial types of fibrosis were found in 4 of these cases. This was associated with demonstrable intimal sclerosis of the smaller arteries in 1 case only, in which infarcts were also present. Scott concluded that it seems unwarranted to attribute these changes to latent myocardial syphilis.

Hines in 1924 reported a case of syphilitic mesaortitis and myocarditis in a patient 32 years old. Grossly the myocardium showed recent and old infarcts and multiple thromboses of the small branches of the coronary arteries. The heart was hypertrophic. Histologically there were necrosis of the cardiac muscle fibers, granulation tissue with newly formed capillaries and many polymorphonuclear leukocytes. Perivascular infiltrations of lymphocytes predominated. Occasionally, fibrous scarring was noted. By the use of the Levaditi method spirochetes were found in the inflammatory areas and around blood vessels. He stated that although these striking myocardial changes are not rare, it is not common for syphilis to produce coronary thrombosis and infarction.

Howard in 1924 stated that in the late stage of syphilis a purely syphilitic myocarditis is not uncommon. In the earlier stages, however, parenchymatous degeneration and proliferation of lymphoid and endothelial cells about branches of the coronary artery and about the vasa vasorum prevail. This paper is based on clinical findings, without postmortem or microscopic observations.

Clawson in 1924 stated that syphilis of the myocardium appears to be rare. Of 9 cases of syphilitic aortitis, 3 showed myocardial fibrosis, and in 2 of these the condition seemed to be the result of coronary sclerosis.

Warthin, in discussing Clawson's paper, said that in his opinion Clawson's failure to find evidence of syphilitic myocarditis lay in the insufficient number of sections cut from the myocardium.

Moenckeberg in 1924 stated that Virchow's simple fibrous form of cardiac syphilis has no characteristic features. Such myocarditis is similar to scars formed as sequels to vascular disturbances. Moenckeberg spoke of gummas and of gummatous myocarditis with giant cells.

Palaase and Despeignes in 1924 reported a case of syphilitic aneurysm of the aorta. The myocardium showed no gross lesions. But the authors believed that they were dealing with syphilitic myocarditis and stated that they would refer to it subsequently.

Vaquez in 1924 classified syphilitic myocarditis as acute and subacute. Acute syphilitic myocarditis is evidenced through an extensive parenchymatous degeneration rather than a true inflammation. Subacute syphilitic myocarditis shows a diffuse, but slight, sclerosis and an interstitial infiltration by round cells which sometimes form miliary gummas around the blood vessels. The fibers of the cardiac muscle may show fatty degeneration or atrophy, or may be fragmented. The interstitial lesion is always associated with endoperiarteritis.

Stadler in 1925 said that interstitial syphilitic myocarditis leads to a slowly progressing, noncharacteristic inadequacy of the cardiac muscle.

Romberg in 1925 gave it as his opinion that damage of the heart in syphilis is not rare, but is rarer than damage of the aorta and coronary arteries.

Dietrich in 1925 stated that anatomic changes in the heart in syphilis are rare. Gummas may be found in the heart in syphilis, or scars as the result of gummas. Sometimes vascular changes are present. Whether the scars are really caused by the syphilitic agent or by something else cannot be decided. Ischemic conditions in other diseases may produce similar scars. The author did not mention the occurrence of a true syphilitic myocarditis.

Lenoble in 1925 stated that there is an interstitial form of syphilitic myocarditis which is characterized by the absence of calcareous deposits. A parenchymatous syphilitic myocarditis also exists, which occurs independent of vascular changes. It is possible that spirochetes either disappear quickly from such areas or do not exist there (myocardites déshabitées). In another paper he mentioned that one of the characteristics of syphilitic myocarditis is its rarity. This is in marked contrast to the frequency of syphilitic aortic lesions.

Maclachlan in 1925 pointed out in regard to a case of syphilitic aortitis which terminated in sudden death, and which was not given postmortem examination, that the sudden death could possibly be explained by the involvement of the coronaries, although the sudden death due to myocardial changes described by Warthin must be remembered.

Young in 1925 described an aneurysm and a gumma in the same heart. No atheroma was found in the coronary artery—a fact which induced the author to conclude that the aneurysm was of syphilitic origin. The left coronary was patent, but at its commencement the opening was flattened. He gave no histologic details.

Leschke in 1925 stated that diffuse interstitial syphilitic myocarditis is not rare in congenital syphilis. Later, however, it becomes rare. Sudden death is not uncommon in syphilitic myocarditis.

Warthin's paper in 1925 will be referred to later.

Guerich in 1925 wrote that of 23,179 autopsies, 806 showed syphilitic changes. Myocardial changes, however, were not mentioned.

Arnett in 1926 in a clinical paper mentioned that there is good reason to believe that during, if not before, the appearance of the secondary rash in syphilis, the spirochetes invade the cardiovascular system. But serious cardiovascular complications during the early stages of syphilis are extremely rare.

Karsner in 1926 said that syphilitic lesions of the heart may be represented either by gumma or by a diffuse chronic interstitial myocarditis. According to Warthin, the latter is extremely common in late syphilis.

Strauss in 1926 observed that syphilis of the myocardium is seen in the form of scattered patches throughout the muscle. The author did not go into histologic details.

Boyd in 1926 reported a case of acute myocardial syphilis. Histologically, lymphocytes and plasma cells were found here and there in relation to blood vessels. Similar collections of cells were present in the adventitia of the left coronary artery. In addition, polymorphonuclear leukocytes were found. The author claimed to have found spirochetes (the pictures of the spirochetes, however, are not typical of Spirochæta pallida).

Warthin in 1926 reported cases, and reached conclusions, similar to those in the paper of 1925.

Price in 1926 stated that fibrosis of the myocardium in syphilis may be the result of coronary disease or of gummas. The author continued:

> Apart from inducing secondary fibrosis in the manner described, may syphilis give rise to fibrosis of the myocardium independently? In other words, is it among the causes of primary chronic myocarditis, i. e., a true inflammation? There is no doubt that syphilis may give rise to a primary chronic inflammation elsewhere; and it would appear that congenital syphilis does so in the case of the myocardium. Some authorities are of the opinion that acquired syphilis may cause a patchy or a diffuse fine fibrosis independently of the coronary arteries, while others are not. In any case, the histodiagnosis is very difficult even in the early stage so that it is probable that many of the cases of fibrosis of the myocardium in elderly people which are thought to be the result of syphilis are not so.

Delafield and Prudden in 1927 found that syphilitic myocarditis is accompanied by growth of connective tissue or by granulation tissue in the wall of the heart between the muscle fibers or in the walls of the blood vessels.

Kirch, in 1927, stated that the possibility of a primary fibrous myocarditis in syphilis is not proved. The syphilitic origin of the changes found in fibrous myocarditis is only probable. Spirochetes have not been demonstrated in such lesions.

Clawson and Bell in 1927 studied the hearts of 28 persons with syphilitic aortitis showing syphilitic involvement of the aortic valve. The hearts were studied carefully. Fibrosis was noted grossly in 1 heart. This heart also showed slight thickening of the coronary arteries, of the senile type. Microscopic areas of fibrosis were seen in 11 of the 28 hearts. The fibrosis was present in slight degree in all but 1, in which it was of moderate degree. The left coronary artery in this case showed a severe amount of senile sclerosis. The type of fibrosis was purely atrophic in 8 of the 11 positive cases. It consisted of atrophy of muscle fibers with replacement by scar tissue, without the presence of leukocytes. This atrophic type of fibrosis is the kind commonly found in old people with coronary injury. In 3 of these 8, slight gross injury was noted in the coronaries. In 3 the fibrosis was proliferative and of slight degree and might easily have been syphilitic in origin. Ten blocks from various parts of the heart of each of the 28 patients were stained for spirochetes by the Levaditi method. With each group of material, a tissue known to be syphilitic was stained as a control. This control material in every case showed many spirochetes, but spirochetes could not be found in any of the 28 hearts having syphilitic aortic insufficiency. The hearts of 15 patients who died rather suddenly were also studied. These hearts showed in addition to syphilitic aortitis a narrowing or a closure of the mouths of the coronary arteries. Gross myocardial fibrosis was not observed in any of these 15 hearts. Infarcts commonly found in cases of senile coronary disease were not present in any of the hearts which had syphilitic narrowing of the coronary orifices. Microscopic myocardial fibrosis was seen in 4 of the 15 hearts, three times in a slight degree and once in a moderate degree. The scars in all 4 were proliferative with lymphocytic infiltration. Ten blocks from each of 13 of these 15 hearts were stained for spirochetes and compared with a known control. Spirochetes were not found in any of the 13. The hearts of 23 patients who died from ruptured aneurysm showed no gross fibrosis. In 4 hearts a slight degree of proliferative fibrosis with lymphocytic infiltration was detected microscopically at the base of the heart. Spirochetes were sought in 22 of these hearts, as in the preceding hearts, but none was found. In 3 instances multiple gummas were found. Of 9 hearts from persons in whom syphilitic aortitis was found accidentally at the autopsy table, none showed gross myocardial fibrosis. Microscopic myocardial fibrosis was present in 3 of the 9 hearts, once in a moderate degree and twice in a slight degree. The fibrosis was atrophic in all.

Morris in 1927 mentioned gummas as sources of cardiac aneurysms in addition to syphilitic changes of the coronary arteries, but he did not give details of the latter changes. Syphilis of the heart assumes

in no way the paramount rôle that the spirochetal infection plays in the production of aneurysms of the aorta.

Henry in 1927, in a clinical note, stated that patients whose chief complaints are attacks of pericardial pains and arhythmia, and who have low blood pressure, low hemoglobin and a one plus or negative Wassermann reaction, are not by any means all syphilitic, but that if no definite pathologic condition is found, it is well to make a therapeutic test.

Heimann in 1927 stated in a clinical analysis of 105 patients that syphilitic myocardial degeneration may occur without valvular mischief and sometimes without thickening of superficial arteries.

Groedel in 1927, in a roentgenologic study, maintained that in syphilitic disease of the cardiac muscle the relatively slight enlargement of the heart is often remarkable. But no proof is brought forward that the cases the author was dealing with showed syphilitic changes in the cardiac muscle.

Scott in 1927, basing his opinion on 75 cases that at autopsy showed syphilitic involvement of the aortic valves, stated that the histologic changes in the myocardium are not characteristic and to regard them as evidence of latent myocardial syphilis is unwarranted.

Schlesinger in 1928 ventured the opinion that in acquired syphilis the myocardium does not show the presence of spirochetes, contrary to the findings in congenital syphilis. He mentioned that disease of the myocardium in syphilis is common.

Lamb in 1928 was convinced that the myocardial changes in syphilis are really changes of great importance. To explain why these changes are not found more frequently, he mentioned that at autopsy it is unusual to take more than one or two pieces of cardiac muscle for study. Under these circumstances only the grossest lesions are seen, and the slighter changes are encountered by chance only.

Harris in 1928, in a paper based on observations of 100 patients (postmortem observations are not included), stated that as a matter of fact syphilis is a common cardiac disease, but unfortunately in the majority of cases not recognized.

To Clawson in 1928 it seemed evident that, even in a slight degree, myocarditis with syphilitic aortitis is rare, and that death, except in a few cases with myocardial gummas, is seldom if ever due to a myocardial inflammatory condition or to myocardial scars resulting from inflammation. He added that proliferative or exudative inflammation in the myocardium is rare in cases of syphilitic aortitis.

Kuelbs in 1928 stated that syphilis of the heart occurs either in the form of a diffuse gummatous interstitial inflammation or in the form of circumscribed gummas. Sclerotic foci with round cell infiltra-

tions, giant cells, gummas, periarteritis, endarteritis and endophlebitis are in the foreground.

Hazen in 1928 declared that it is becoming a matter not only of clinical, but also of autopsy record that the heart is frequently involved in syphilis. He often quoted Warthin, but did not offer cases of his own.

Reid in 1928 said that in recent years there has been an appreciation of the fact that coincident with the syphilitic lesion in the aorta, the heart proper is usually involved. Grossly, dilatation, hypertrophy, atrophy and patches of fibrosis in the wall of the left ventricle are often noted. He quoted Warthin frequently.

Arnett in 1928 described 2 cases of early syphilis in which death occurred from septicemia. He could not demonstrate spirochetes in the hearts. The sections also showed nothing characteristic of syphilis. He stated, however, that the changes in the myocardium due to the septicemia might have interfered with fine pathologic changes that could have been attributable to syphilis. He was unable to demonstrate organic cardiovascular disease in 25 patients afflicted with syphilis in the secondary stage.

Krumbhaar in 1928 remarked that syphilitic interstitial myocarditis probably occurs much more frequently than is generally supposed, but that unfortunately it is often difficult or impossible to differentiate syphilitic fibrosis from other forms of fibrosis.

Cookson in 1929 reported a case of cardiac syphilis with ventricular aneurysms occurring in a woman 43 years old. The heart showed a pale, slightly softened myocardium. Three aneurysms occupied the posterior part of the base of the left ventricle. On section it was noted that the walls of the aneurysms consisted of fibrous tissue containing considerable deposits of calcium. The valves were normal. There were slight, atheromatous changes in the aorta. A branch of the circumflex division of the left coronary artery was obliterated. Histologically, the aneurysmal wall showed necrotic tissue, bounded by dense fibrous tissue, which was infiltrated with plasma cells and lymphocytes. The plasma cells predominated. The blood vessels in the degenerated area showed marked obliterative changes, and, in some instances, the lumina were occluded. In spite of the finding of coronary sclerosis with obliteration of one of the coronary branches, the case is reported as one of cardiac syphilis.

Benson in 1929 described the case of a man, 66 years old. There were mild syphilitic changes in the aorta. The coronary ostia were patent, but the coronary arteries were sclerotic. The myocardium showed areas of necrosis and semitranslucent strands of fibrosis. The heart was the seat of a ruptured aneurysm. Histologically, lymphocytes were found in the adventitia of the coronary arteries. Their

lumina were almost completely occluded by a fibrous thickening of the intima. The media was infiltrated by lymphocytes. Atheromas and calcification were almost lacking. The myocardium showed necrotic portions. A perivascular infiltration of the interstitial tissue was not prominent. The necrotic portions in the myocardium were called gummas. The author believed that his case was similar to the cases of syphilitic myocarditis described by Warthin.

Cowan and Faulds in 1929, in a paper on syphilis of the heart and aorta, held that syphilitic endarteritis of the adventitial vessels of the aorta and of the arteries of the heart plays an important part in the causation of aneurysms and of ischemic fibrosis of the myocardium. There are several specific myocardial lesions, but in the majority of cases the myocardial lesions are only side issues, the result of coronary disease and so in no way specific. Diffuse fibrosis (subacute interstitial fibrosis) has been found during the secondary stages in the adult, and more often in congenital syphilis in infants and young children. As a result of occlusion of the orifices of the coronary arteries or of narrowing in their course by specific endarteritis, an infarct may occur or a para-arterial fibrosis may result. The ultimate lesions in the muscle are not syphilitic, though they have a syphilitic cause.

Lukomski in 1929 stated that the damages of the aorta and heart in late syphilis are the results of vascular changes in early syphilis.

Levine in 1929 remarked that syphilis is not a common cause of coronary thrombosis. Four and one-half per cent of the cases of coronary thrombosis were syphilitic. But it does not follow that even in these syphilis had a direct causative influence.

Simpson in 1929 pointed out that there is a lack of agreement as to what constitutes the histologic picture of cardiovascular syphilis. He was of the opinion that syphilitic myocarditis is a common disease. He stated that identification of spirochetes in the tissue furnishes conclusive evidence of the disease.

Templeton in 1929 remarked that myocardial changes are due to coronary blockings, and that the whole myocardium may be actually involved by the spirochetes.

Gravier in 1929 classified syphilitic myocarditis as mechanical lesions brought about by an obliteration of the coronary arteries and as inflammatory lesions (myocarditis, subacute and chronic). The author described the case of a woman 44 years old. She presented syphilitic aortitis and an enlarged heart with open mouths of the coronary arteries. The myocardium, grossly, revealed no changes. Histologically, the myocardium showed an interstitial connective tissue reaction, with marked inflammation and edema. Many plasmatocytes were spread between the muscle fibers. The capillaries were apparently dilated. Other fields showed greater dissociation of the muscle fibers, and the

connective tissue was more marked. The cellular infiltration here was more or less pronounced. Other portions revealed that the connective tissue had not only spread apart the muscle fibers, but also had formed actual bands of fibers. There were many capillaries in these fields, but only a few of the arterioles were the seat of endarteritis. The author stated that subacute syphilitic myocarditis may show large fibrous lesions grossly, but that more often the lesions are detectable only by the microscope.

Brugsch in 1929 made the statement that the results of the studies of Grassmann, who found abnormal heart rhythms in 15 per cent of 288 patients with early syphilis, do not indicate a serious involvement of the heart. In the late stage of syphilis involvement of the heart is rare as compared with involvement of the aorta. Syphilis may present itself in the form of myocardial scars resulting from syphilitic arteritis of the coronary branches, or it may produce the myocardial lesions directly.

Wilson in 1929 described the case of a man 44 years old, with clinically a complete heart block. The heart with the aorta weighed 940 Gm. The papillary muscles were enlarged and sclerosed. The coronary vessels were enlarged, their walls thickened. The aorta showed syphilitic aortitis. The cardiac muscle, histologically, revealed patchy areas of sclerosis and an infiltration of round cells in the interstitial tissue. By the use of the Levaditi stain spirochetes were demonstrated in the interventricular septum. They were found just below the aortic valve. The author made the diagnosis of syphilitic myocarditis. Pictures of spirochetes are not shown.

Hajóshi in 1929 described the case of a patient whose heart, in the author's opinion, showed gummas. The case, however, showed, in addition, tuberculosis of the lungs and lymph nodes and a caseous tuberculous pericarditis.

Dennis in 1930 remarked that the myocardium in late syphilis shows rather constantly perivascular foci, identical with perivascular foci seen elsewhere in syphilis. A various degree of reparative fibrosis and its secondary effects can also be found. He believed that death results more particularly from syphilitic aortitis with its accompanying aortic insufficiency, from aneurysm or from coronary occlusion.

MacCallum in 1930 stated that there is a tendency to ascribe the final failure or decompensation of the heart in cases of syphilitic disease of the aorta and the aortic valves to a corresponding disease of the myocardium. He had seen few cases in which active syphilitic myocarditis was suggested, and he was unable to feel sure that scars found in the myocardium were syphilitic. Nevertheless, that syphilitic disease of the myocardium could occur in the form described by Warthin he thought was fairly self-evident, and that it would heal with the traces indicated by such scars was equally clear.

Warthin in 1930 described the case of a 24 year old man with extensive syphilitic myocarditis associated with malignant syphilis. The heart showed grossly a slight yellowish striping. The coronary arteries appeared normal. Histologically, there were fatty degeneration and infiltration of the myocardium, increase in interstitial nuclei, proliferation of fibroblasts, reticulo-endothelial cells and interstitial edema. There was infiltration by plasma cells and lymphocytes, showing a typical "single file" arrangement, characteristic of syphilitic myocarditis. Monocytes were also present and a few polymorphonuclear leukocytes. There was a perivascular aggregation of cells around smaller branches of the coronary vessels. The larger aggregations could be styled as miliary gummas, but in general the process was rather diffuse. The muscle fibers were as a rule atrophic. Fragmented spirochetes were seen, broken into portions with two or three spirals. A few perfect spirochetes were found, one in a giant cell.

Chaniotis in 1930 reported the case of a man 47 years old. The diagnosis was syphilitic aortitis with diffuse sclerotic myocarditis. Microscopically, the heart showed diffuse connective tissue proliferation, with degenerative changes, and edema. The coronary arteries did not show changes that could explain the myocardial lesions. Chaniotis therefore believed that his case was one of primary syphilitic myocarditis. It was called primary to differentiate this form of myocarditis from myocarditis secondary to vascular changes. He stated that if in such cases spirochetes cannot be found, the diagnosis of syphilis can be made by the existence of other clinico-anatomic factors.

Cowan in 1930 remarked that diffuse fibrosis, subacute interstitial fibrosis, has been found in the secondary stages of syphillis in the adult and more frequently in congenital syphilis in infants and young children. But the most important and the most frequent sequel of syphilis is due to syphilitic disease of the coronary arteries and ischemic fibrosis. The arteries may be narrowed or occluded at their orifices by a syphilitic plaque in the aorta, or in their course by a specific endarteritis obliterans. Infarct or para-arterial fibrosis results. The ultimate muscular lesions are not specific, though they have a specific cause.

Coombs in 1930, in an address on cardiovascular syphilis, dealt mainly with syphilitic aortitis and syphilitic aortic insufficiency. He mentioned that the coronary orifices are sometimes "nipped in a tightening grasp," the result being starvation of the muscles which they supply, with replacement fibrosis and degeneration of the myocardial fibers.

Coombs in 1930 also described hearts of persons showing syphilitic aortitis. Many hearts showed evidence of malnutrition. Often an increase in connective tissue was seen, with little or no inflammatory

reaction. In 1 heart, a granulomatous focus was observed. In some hearts, the author described a weak cellular response—a few plasma cells and lymphocytes—drowned in serum, which gave the tissue a dropsical appearance.

Clawson in 1930 mentioned that in rare instances syphilis causes gummas of the heart or diffuse exudative and proliferative inflammations within the myocardium.

Bell in 1930 stated that syphilis of the myocardium is rare. Patches of fibrous tissue in the myocardium are generally due to coronary disease; but syphilis is to be considered if there are large numbers of lymphocytes.

Martland in 1930 reported an investigation based on observations in the myocardium in 101 cases of syphilis of the aorta and heart, in which death had occurred suddenly, and in which autopsy was performed. The myocardium in these cases was usually normal or showed only slight or moderate hypertrophy. No evidence of specific myocardial lesions was noted. In a few cases, the heart was small, and the myocardium the seat of brown atrophy. In none of the cases was there any evidence of specific myocardial lesions sufficient to explain death. Any lesion in the myocardium, besides hypertrophy and occasional brown atrophy, is usually interpreted as due to superimposed arteriosclerosis of the coronaries. The author concluded that syphilis involving the heart in portions other than the region of the aortic valve is unusual and is not of great clinical or pathologic importance.

Carr in 1930 studied the gross changes in the heart in 119 cases of cardiovascular syphilis. He found that, except for a predominant left ventricular hypertrophy that resembles that of essential hypertension, the gross myocardial changes associated with syphilitic aortitis are not characteristic.

Maher in 1930 reported the microscopic lesions of cardiac syphilis in 5 cases of uncomplicated and probably untreated syphilitic aortic regurgitation. He stated that the inflammatory reaction, presumably due to syphilis by exclusion of other factors, was found to be a lymphocytic and plasma cell infiltration about the coronary arteries and their branches and beneath the visceral pericardium. In the muscular tissue, the invasion appeared between the fibers and could be demonstrated about the capillaries. In the discussion, the author stated that the coronary arterial picture is the same in syphilitic lesions as in lesions in other cases, namely, an infiltration by round cells about the vessels. He did not demonstrate spirochetes in the myocardium, although he thought that they were there.

Paullin in 1930 reported two cases of syphilitic myocarditis. The first case showed, microscopically, numerous areas of degeneration in which the cardiac muscle had been completely replaced by bands of

fibrous tissue, and there were numerous collections of lymphocytic infiltration scattered here and there throughout the muscle and about the arteries. Occasionally, fibroblasts and plasma cells were visible in these fields. The second case showed a marked infiltration by lymphocytes, plasma cells and polymorphonuclear leukocytes, with complete destruction of the cardiac muscle. There was also evidence of fibroblastic proliferation and edema. Other areas were noted in which there was an old fibrosis with replacement of the cardiac muscle by bands of connective tissue. Sections from this heart were examined by Dr. Warthin, who demonstrated spirochetes in the areas of syphilitic inflammation.

Moritz in 1931, in a paper on syphilitic coronary arteritis, did not mention an involvement of the myocardium.

(To be concluded)

THE ETIOLOGY OF CANCER

III. MISCELLANEOUS FEATURES *

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NUCLEAR ABERRATIONS

Nuclear Fusion.—With cellular reproduction forming such an outstanding part of the phenomena of cancer, and especially in view of the fact that nuclear abnormalities are such a conspicuous feature of its morphology, it was only to be expected that among the theories of the causation of cancer would be those explaining this by nuclear aberration. A number of such theories have been advanced, the principal ones of which would explain cancer either as the result of acquisition of abnormal properties by the cell as the result of nuclear fusions, or as being due to the loss by the nucleus of those factors determining regulation of growth. Of these two principal and divergent theories, that of nuclear fusion is the older. In 1887 Karg advanced the idea that the unlimited reproduction of cancer cells was to be explained by such a mechanism, and in explanation of their extreme capacity for migration with survival, he suggested that the other element entering into the fusion was the leukocyte, so that the offspring of this union showed not only features characteristic of the original cells of the cancerous tissue, but in addition to the newly achieved properties of excessive reproduction, those of ability to infiltrate and metastasize. Klebs shortly afterward promulgated quite independently the same theory, and Schleich almost simultaneously expressed the view that in nuclear fusion was to be found the explanation of malignant growth, but did not attempt to identify the cells contributing the added nuclear material, regarding these as being possibly at times those of another individual. Shattock and Ballance had already taken a somewhat similar view and had described in cancer cells karyorrhexis with extrusion of nuclear fragments, which they suggested might function in a manner similar to the fertilizing action of spermatozoa. Morpurgo in 1894 expressed the view that the intracellular inclusions, which about that time were exciting much interest because of their frequent identification as protozoan parasites, in reality represented chromatophil material which was attracted to dividing nuclei, a view essentialy similar to that of Shattock and Ballance, although without the etiologic implications of the latter.

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In 1903 Farmer, Moore and Walker described heterotypic mitoses in cancer cells, with a reduction of chromosomes similar to that of sex cells, and Farmer observed what he regarded as evidences of fusion in such cells, while Bushnell suggested that their growth might rest on a parthenogenetic basis. The observations of Farmer and his colleagues received corroboration by Bushnell and Cavers, Bashford, and Bashford and Murray, and excited a considerable degree of interest, although their significance was variously interpreted. Campbell, for instance, regarded the change as one of reversion to a primitive type of cell characterized by having a reduced number of chromosomes—an idea of reversionary metamorphosis that was not particularly new as applied to cancer, as it had been advanced by Gresswell in 1887. Although Farmer, Moore and Walker described what they regarded as evidence of nuclear fusion in cancer cells, and particularly with nuclear material of leukocytic origin, they were careful to state that such evidence of fusion had not been found in connection with heterotypic cells, however attractive such evidence would have been in support of their theory. Bashford, basing his opinion on the fact that despite the recurrent presence of nuclei with reduced chromosomes, this reduction did not reach beyond one half of the normal somatic number, expressed the view that nuclear fusion would be necessary to keep reduction within these bounds. Other later advocates of the cellular fusion theory have been Hallion, in 1907, and Welsh, and Kotzenberg as lately as 1922. Practically all the writers cited previously took the view that the fusion was between cells of the same individual, but Kronthal, writing in 1906, considered that the fusing element was from another, and even more extreme speculations have been advanced by Evans, Shannon and Stefani, with the hypothesis that cells of parasitic protozoa were concerned. Aichel in 1911 advanced a fusion theory based on the relatively independent ground of the work done on sea-urchins' eggs by Boveri, in which multiple fertilization was found possible. An ingenious suggestion as to the cause of the varying properties of benign and malignant tumors was embraced in the theory as advanced by Aichel, to the effect that while the conspicuous properties of malignancy were the result of fusion of somatic cells with leukocytes, benign tumors were the product of fusion of somatic cells alone. Another rather ingenious variant of the cell fusion theory was that of Skerrett, who, not satisfied with leukocytic fusion as adequate ground for malignant behavior, would have these cells serving as carriers for germ cell idioplasm to the cells the fate of which was to become cancerous. It was not long after the earlier publications of Farmer, Moore and Walker that their results, or more particularly their observations, were questioned. Bashford and Murray in 1906 reversed their former corroboratory opinion; Dor expressed his doubt of the validity of their

observations, and in 1910 Howard and Schulz, and Deton, reported that they were unable to verify them.

Nuclear Reduction.—As opposed to the theory of nuclear excess, or of restoration to normal chromosome value by fusion, are the several theories that would explain cancer by loss of nuclear material, and so of factors determinant of normal cellular behavior. Strictly speaking, in large part these theories, and especially the anaplasia theory of von Hansemann, are explanations of the mechanism of cancerous growth rather than of its origin. The first promulgation by von Hansemann of his theory appeared in 1890; essentially it stated that in every asymmetric cell division there occurs an alteration in differentiation, with possible corresponding alterations of growth energy and growth direction. From asymmetric division two types of cell might result—those with fewer nuclear segments, capable only of limited further growth and reproduction, and others with unrestricted and actually unrestrained powers of further growth. As distinct from the theories that would regard the cancer cell as one showing embryonic reversion, von Hansemann pointed out that cells showing this anaplastic change differ from embryonic cells, which are the possessors of undeveloped potentialities in the way of differentiation, as in the anaplastic cells differential potentialities are completely lost. The principal objections to von Hansemann's theory have been on the grounds that asymmetric mitoses are not exclusively peculiar to cancerous tissues, Stroebe having reported their occurrence in normal regenerative processes and Krompecher in embryonic tissues, and Häcker having found that a number of agents might induce their appearance. But as pointed out by von Hansemann, it would be only in the occasional case in which asymmetric division entailed the loss of the growth-regulatory mechanism without serious impairment of cellular viability, that malignancy would result. In many respects similar to the theory of von Hansemann is that of Boveri, who likewise believed that the peculiarities of cancerous behavior could be explained by loss of nuclear material with corresponding loss of cell regulation. In experiments conducted on sea-urchins' eggs, Boveri found that such loss might be caused by irritants of the type known to cause cancer, thus adding an etiologic element to the theory which was absent in von Hansemann's speculations. Rockey would explain irregular mitoses as the result of repeated interference with normal regeneration, along with cellular displacement, the two combined eventually leading to hyperkaryokinesis and distorted nuclear activity. An excellent summary and discussion of von Hansemann's theory is that of Whitman, who in 1920 advanced the view that the cancer cell is a new variety of cell, which originates by somatic mutation through interference with mitosis—an idea essentially similar, though expressed in different terms, to that of Rockey—and views

similar to those of von Hansemann have been published by Oertel, by Perthes and by Levy.

The view of cancer as the result of a reversionary metamorphosis, alluded to in connection with Campbell and Gresswell, was advanced by Gilchrist in 1909, and again by Campbell in 1920, with the added suggestion that it represents an abortive attempt at asexual reproduction similar to that of lower orders of animal life. The more usual view is to regard cancer as a reversion to a sexual type of cell; this was suggested in connection with the work of Farmer, Moore and Walker already cited, and Walker in 1905 called attention to the similarity of Plimmer's bodies to the archoplasmic vesicles seen in spermatogonia, again with the suggestion of phylogenetic reversion. And again in 1911 Walker and Whittingham called attention to the analogies between the nucleus of the cancer cell and that of the sex cell. A not dissimilar view, but with closer kinship to Cohnheim's hypothesis, is that of Beard, who, largely on the grounds of nuclear peculiarities in cancer, regarded neoplastic cells as resulting from the displacement of primary germ cells—a hypothesis that Grünbaum believed to be confirmed by the findings of Farmer and his co-workers.

Other attempts to explain the phenomena of cancer by various types of assumed nuclear aberration are: that of Fabre-Domergue, who would ascribe carcinoma to a lack of relationship of the planes of nuclear division to body surfaces, so that the epithelial cells no longer arrange themselves, nor regulate themselves, with relation to those surfaces; a somewhat similar theory of Forbes-Ross, who also regarded the fundamental change in the cancer cell as one of lost polarity; that of Jessup, who would regard cancer as due to external stimuli effecting a disturbance of intracellular electrical equilibrium, with resultant loss of nuclear symmetry. Ries believed that cancer resulted from nuclear injury; Ariens-Kappers suggested that malignant growth centered in centrosomic disturbance, since the centrosome is regularly to be found on the side most exposed to irritation; Lumiere would ascribe malignant growth to unduly prolonged exercise of the function of regenerative reproduction. Robertson and Heiberg believed that the excessive proliferative rate of malignant tissues is the result of a disturbance of the normal ratio between nucleus and cytoplasm, which Sokoloff found to be low in cancerous cells, the essential change, according to Robertson, being the production of cells capable of dividing at abnormally low relative amounts of nuclear material as compared with the amounts of cytoplasm. Heiberg, on the other hand, would regard the fundamental change as one of increase of nuclear volume, not necessarily associated with an altered nucleocytoplasmic ratio, since the volume of the cytoplasm might also be increased, but with an alteration of chromosome content by virtue of which the cells suffer a permanent

alteration of growth energy; in small cell tumors an actual increase in nucleocytoplasmic ratio, overloading the cells with nuclear material, would force them to rapid and sustained division.

To some extent, the relationships between nuclear irregularities and malignant growth have lent themselves to more or less experimental study, in connection with tissue cultures. In 1913 Lambert reported that atypical mitoses were to be seen in cultures of sarcomatous, but not in those of normal, tissues. Mottram, reporting on experiments with cultures of renal tissues of the normal rat, observed that with a normal carbon dioxide tension of 40 mm., nuclear division was frequent, but that with considerably higher tensions the mitotic figures became abnormal, with frequent irregular migration of the chromatin. Goldschmidt and Fischer in a study of nuclear division in cultured carcinomas from mice, published in 1929, found pronounced irregularities in the way of multipolar mitoses only very rarely, but the chromosome count in the great majority of mitoses was less than normal, ranging as a rule from 32 to 36, as compared with the normal somatic count for the mouse of 40.

As regards observations on excised tumor tissues, Evans reported that for any accuracy immediate fixation of the material is absolutely essential, and that if this is prompt, most nuclear figures will be found to be normal. In these circumstances he observed occasional tetrad chromosomes, but no reduction below the normal number. With the exception of this work, there is no evidence that can be regarded as contradictory to von Hansemann's theory of anaplasia; but this, as has been suggested, and as was acknowledged by von Hansemann himself, is not an explanation of the etiology of cancer, but rather of the mechanism through which malignant growth may be achieved.

NEUROTROPHISM AND CANCER

In connection with the subject of the tar cancers, reference has been made to possible influences of trophic nervous changes on cancerous development. As a matter of fact, such influences have been suggested as the actual determining factor in the causation of cancer. Lang in 1879 suggested that cancer might originate on such a basis—a suggestion that was renewed by Dieffenbach in 1906—while Hodgson in 1905 advanced the idea that persistent nerve fatigue was the cause, and Kölner in 1907 regarded cancer as resulting from the release of cells from central control, either nervous or humoral. Masani also, in 1911, ascribed the disordered growth of cancer to the lack of an organizing, regulating mechanism normally contributed through the nerves. Stajano in 1922 ascribed cancer to trophic causes, arguing from the relations between surface cancers and trauma, and the alleged

liability of cancer to develop in sites normally abundantly innervated. Engel would explain the action of cancerogenic chemical agencies by their action on the local nerves, and Molotkoff, on the basis of a very similar view, suggested neurotomy as a means of treatment, and believed that with this he was able to influence the course of cancer favorably. A less direct influence is assumed by Lorin-Epstein and Bondartschuk and by Willy Meyer. The former would interpret the influence of nerves in the development of cancer as in the nature of a general effect, acting in addition to definitely local cellular factors. The view of Meyer is not dissimilar, in that he regarded salt imbalance as one element in the causation of tumor, and believed that in part this may be achieved through sympathetic nervous disturbance. That there is a frequent correspondence between the growth area of superficial cancers and the distribution of sensory innervation has been particularly emphasized by Cheatle with reference to facial cancers.

As to the experimental study of cancer, this has contributed a certain amount of information, sometimes conflicting, as to the influence of innervation on the causation or progress of cancer. The possibility that nerve mechanism is fundamentally involved in the former can be considered as definitely excluded by the indirect evidence afforded by the experimental induction of malignant growth in conditions entirely free from nervous elements, as in the cultured tissues of Fischer and Laser. On the basis of observation of already initiated cancers, there is certainly no antagonism between innervation and cancerous growth. Begg found that not only may tar cancers invade nerve cords, but that these may actually afford ready paths for the farther growth of the neoplasm, and in a recent article Meissel and Larionow reported the effects of implantation of a transferable carcinoma of the mouse into a severed nerve cord. Not only was there an absence of antagonism between the two, but an actually redundant regeneration of nerve fibers occurred, with growth into the tumor to form plexuses about the tumor lobules, and with the penetration of single fibers even more intimately into the cancer. As to the natural relations of nerve fibers to malignant tumors, the testimony is not altogether concordant. Nakamoto and Tsunoda both reported an absence of nerves in tar cancers, and the former stated that in the course of development of these cancers there is a relatively early disintegration of the peripheral nerves. On the other hand, Itchikawa, Baum and Uwatoko, and Herzog, using principally silver impregnation methods, were able to demonstrate what appeared to be nerve filaments in the stroma of the tumors studied, and Oertel reported finding them within a number of carcinomas and sarcomas.

As concerns the effects of nerve lesions on the development of cancer, the work of Auler, Itchikawa, Kotzareff, Remond, Sendrail

and Bernardbeig, and Cramer, has been cited in connection with the tar cancers. Since their work, similar results have been obtained by Heim and Tinozzi, and Tsunoda, and recently by Eiger and Czarnecki, all of whom observed evidence that sympathetic innervation exerts a restraining influence on the growth or development of tumors. Hirsch-Hoffmann, too, has observed that the repeated injection of sympatheticotropic ephedrine or adrenalin causes increased growth of tumors. That the effect, however, is principally achieved through altered nutrition and is less concerned with the induction of tumors, is suggested by the experiments of Aschner, who found the hyperemia that followed section of the nerve supply of the extremities accelerated the growth of tumors implanted there, and those of Pearce and Van Ailen, who observed enhanced growth of transplanted neoplasms after cervical sympathectomy. As to the work of Molotkoff in which he reported favorable results after resection of nerves in human cancers, Ssokolow, with similar material, was quite unable to confirm it.

HEREDITY AND CANCER

Efforts to determine the effect of heredity on the incidence of human cancer have yielded results which at most must be regarded as indecisive. An analysis of parental histories made by Paget in 1866 showed among the parents of cancerous persons an incidence of that disease of 24.2 per cent, and in 1878 Cripps in a similar study found that practically identical relations obtained between the general incidence of the disease and that in which there was present the direct hereditary relationship —29 and 29.1 per cent, respectively. The incidence rates reported by Williams in 1884 were very similar, but they showed marked disparity in the hereditary element as concerned cancers of various organs, ranging from a frequency of cancerous parental history of 23.7 per cent in cases of uterine cancer to one of 3.3 per cent in cases of skin cancer. Hutchinson in 1886 reported the interesting observation, which has been supported by later observations, that in most cases of the occurrence of carcinoma at an early age, there is a definite history of ancestral cancer.

But while in general the analyses of the relations of cancer at least to immediate heredity failed to show any definite connection, there were collected a considerable number of instances of familial cancer so striking as scarcely to admit explanation on the grounds of coincidence. Among these is the famous example reported by Broca, of a cancerous mother all of whose daughters died of the disease, and with a total of 15 cases among 26 persons belonging to 3 generations. Other cases of generally similar character have been reported by Hardman, Bodilly, Fere, Rebulet, Power, Nason, Williams, Smith, Watkins and Jullien. In practically all of these the cancers were in part at least heterotopic,

although in the family described by Watkins there was a repeated occurrence of rectal cancer, and with this was associated a particular frequency of rectal disease in general. In the example reported by Fere, in which the cancers were practically entirely mammary in location, there was a definite association of agalactia. Although the majority of those making these early reports on cancerous families were firmly convinced of the hereditary character of familial incidence, this view was not generally accepted. Pearson in 1904 expressed the belief that the evidences of a hereditary relationship were so slight as to come within the bounds of random sampling; von Hansemann took the view that at most there might be a barely possible element of hereditary predisposition, and Ledoux-Lebard regarded the instances of reported familial occurrence as purely fortuitous. In addition to data similar to the type cited, one or two studies tended to show what might be regarded as a racial distribution of cancer. Kruse in 1901 found a markedly greater rate of cancer mortality in northern than in southern Italy—a difference that he believed to be of racial origin—and Lyon in Buffalo made the interesting observation that cancer there was most frequent in families of Germanic stock. Madden reported that while cancer in Egypt is common among the Arabs and Copts, it is rare in Negroes. To what extent these racial differences may be due to differences in habit or in living conditions is not known.

In later years there have been reported a considerable number of instances of familial cancer. Warthin in 1913 reported a number of these, and commented on the fact that when in a single generation there occurred several cases of cancer, there was almost certain to be a history of ancestral cancer, and he confirmed Hutchinson's earlier observation that these cancers are likely to develop at an early age. Manson in the same year published an account of the associated occurrence of sarcoma in a mother and her 2 children, and Peiser in 1915 reported 2 instances of cancer families. More were reported by Peller in 1922, and Wassink in 1924 found that among 258 cases of mammary cancer, 76 were associated with similar cancers in other members of the same family. Kaiser in 1924 described a family with a marked predisposition particularly to gastric cancer; Letulle reported several cases of familial cancer, and Swoboda 1 instance. In respect to the number of generations traced, few of these accounts compare with that published by Warthin in 1925, in which, among the offspring of a cancerous great-grandfather, there was an incidence of malignant disease of 18 per cent of the offspring, or 31.8 per cent of those who had attained adult life. There was a marked tendency to gastro-intestinal cancer in the males and to cancer of the organs of generation in the females, with the strikingly early average age of incidence of 37.9 years. Ledo in 1927 described a family that showed an exceptional tendency

toward squamous cell cancers. On the other side of the picture are the families described by van Dam, in which in 12 instances traced for 4 or 5 generations there was no indication of cancerous inheritance, and the observation that in 15 families in each of which both parents had died of cancer, none had occurred among 45 children who had attained the usual age for the appearance of cancer.

While, in general, the data on human beings have left dark the matter of hereditary influences in the causation of cancer, there is a mass of accumulated data, obtained from observation of animals, that is of very definite character. Among the earlier instances of the occurrence of cancer in lower animals on an apparently hereditary basis was the observation by Eberth of spontaneous cancer in 3 offspring of a single pair of white mice, and that cited by Williams, of the occurrence of melanosarcoma in the descendants of a white stallion that had itself died of that disease; but this case might be explained by the peculiar relation that is known to exist between absence of pigmentation and the occurrence of these tumors in horses. In 1900 Loeb and Jobson reported the focal occurrence of bovine cancer on a Wyoming ranch, and in 1903 Voges described similar findings in the Argentine, with the added observation that these cancers occurred in pure white-headed Hereford cattle. Loeb took the view that such foci were to be explained on the basis of heredity, and suggested the same explanation for the so-called "cage epidemics" that were being reported from time to time among white mice.

The laboratory study of the relationship was first pursued from the point of view of susceptibility to implantation of tumor. In 1907 Tyzzer, in connection with an observed apparently hereditary tendency to the development of spontaneous tumors of mice under his observation, believed that this tendency was associated with an immunity to the transplantation of tumor, and Haaland observed that different strains of mice varied greatly in their susceptibility to the implantation of specific tumors; but he made the additional observation that in conditions of altered environment this variation tended to disappear, and eventually his imported mice behaved exactly like those of his original stock. Although, according to Gierke, the influence of heredity in this relationship was minor in effect compared with that of environment, Tyzzer was able, in a later paper, to show that at times liability to successful implantation of tumor was almost entirely a matter of inheritance. An investigation of this subject was made in some detail by Levin in 1911 and again by Loeb and Fleisher in 1912, and these observers agreed with Tyzzer that heredity exerted a marked effect—according to Levin, in accordance with mendelian laws; according to Loeb and Fleisher, if in accordance with mendelian principles, there is necessary an assumption of the existence of multiple factors. McFarland and

McConnell in 1913 likewise found that in different strains of mice there was varying susceptibility to the transplantation of different tumors, and in 1915 Tyzzer reported on a strain of Japaneze waltzing mice in which only 0.39 per cent escaped in the course of 8 years of successive transfers, while common mice were completely insusceptible to the particular tumor used. In the first generation of hybrids only 5 per cent succumbed to the transplanted tumor, and later hybrid generations were almost completely immune. As to the relations of this hereditary insusceptibility to mendelian principles, Tyzzer, like Loeb and Fleisher, believed that this was a matter of factor-complexes. The relationship is certainly not a simple one, as Lathrop and Loeb found that at times hybrid animals may show a high, at times an intermediate, and occasionally a low, rate of susceptibility; Morpurgo and Donati observed that with a resistant stock of animals, the first generation of offspring of susceptible exceptions showed no higher incidence of "takes" than did those of the nonsusceptible animals—indicating for susceptibility the cooperation of other factors than those of hereditary character alone. In contrast with the findings of Lathrop and Loeb, and with those of Tyzzer, Lynch reported an instance of susceptibility to transfer that behaved like a mendelian dominant. Roffo reported an observation of rats in which susceptibility to implantation of tumor was associated with inherited color characteristics.

There is of course little evident relationship between the problem of the hereditary character of susceptibility to transfer and that of the causation of cancer, except to the extent that the inception of cancer would in part be dependent on factors that might be necessary to permit the survival of cells already become malignant. Even in this connection, the results obtained with introduced tumors of foreign origin would have to be interpreted with the reservation that as they do not represent the cells of the individual concerned, their relations may well be quite different from those of the host's own cells after these had become neoplastic.

Of much more direct significance are the experiments that bear directly on the hereditary transmissibility of a predisposition to cancer. Tyzzer, as has been mentioned, believed as early as 1907 that he had observed a distinctly hereditary tendency toward spontaneous tumors in mice, and although Bashford a year later believed that there was no definite evidence of such tendency shown either in the tumors of man or those of lower animals, Thorel in that year reported that he had seen the occurrence of 14 spontaneous tumors within 1 year among 60 mice of the same descent. More instances of "cancer families" in mice were reported by Tyzzer in 1909, and Cuenot and Mercier, dealing with this phase of the etiology of cancer, expressed the conclusion that while cancer in mice might be in part of hereditary origin, it was not

controlled by mendelian characteristics. In 1911 Bashford reported on experiments that reversed his former view, and Murray also described what was evidence of hereditary predisposition to cancer in mice. Henke in 1913 reported on an epidemic of cancer in mice, which appeared to rest definitely on a hereditary basis, and in that year Slye began her publications of the pedigrees of mice, which clearly showed the now undoubted relation between spontaneous tumors of mice and heredity. In 1914 she announced that of the 155 spontaneous tumors that she had observed in mice of which the ancestry could be traced, 146 occurred in circumstances of familial involvement, with some of her strains showing a cancerous incidence as high as 44 per cent. Lathrop and Loeb in 1915 found that the tendency toward tumor development in mice was associated with other recognizable hereditary characteristics, such as color, and that in addition to the element of appearance of spontaneous tumors there was another, entirely independent one—that of the age at which these tumors were most likely to appear. This observation has been recently confirmed by Turdeen. In crossed strains the results were not predictable, as some hybrids showed incidence rates corresponding to the higher parental rate, some an intermediate rate, and some the lower parental rate of incidence. In 1916 Slye published results that indicated clearly the homeotopic character of much of the hereditary tendency toward tumor development, as tumors of specific organs, and further of certain types, occurred repeatedly in certain strains, although rarely otherwise—particularly with reference to a strain of mice with an extraordinarily frequent development of the otherwise rare primary carcinoma of the liver; in 1919 she published similar data pertaining to primary tumors of the testis, of which she had seen, among 19,999 mice which had died of natural causes, 28 cases, all in 1 strain of mice or its hybrids.

While it may be regarded as firmly established that heredity, as studied in lower animals, plays a large part in the incidence of spontaneous tumors, the exact character of the hereditary element is still a matter of dispute. Loeb in 1920 expressed the belief that susceptibility to spontaneous cancer is, like that of inoculability with transplanted tumors, of mendelian type, but explicable only by the assumption of multiple factors. In 1922 Slye published results that would show that cancerous and noncancerous tendencies were transmitted as unit characters, which could be isolated in unit strains, and in 1926 she published additional data tending to show that tumor heredity was of mendelian character, with resistance as the dominant factor, with the tendency toward spontaneous tumors, both as to type and location, behaving like mendelian recessives. In 1928 appeared a report by her on a stock of Japanese waltzing mice which showed an incidence of thyroid carcinomas that she regarded as in strict accordance with the laws governing

mendelian recessives. Lynch, working with spontaneous and induced tumors of the lungs in mice, in 1926 reported that the spontaneous tumors showed a definite hereditary tendency with some indications that this was of dominant character, and in a report a year later on the development of tumors of the lungs in tarred mice, he found that the tumors in these circumstances appeared with relations that again fitted in with the action of a dominant factor. In 1928 Little criticized Slye's interpretation of her results in the belief that the incidence of tumors in her hybrid animals was too high to accord with the conception of mendelian recessivism. He suggested that the tendency to mammary cancer might be explained as a sex-limited mendelian dominant; the fact that Slye's results were too low to fit this concept without adjustment he met by the assumption that in homozygous forms this factor might be of lethal character. Some color is lent to this view by the observation of Stark of the occurrence of epithelial tumors in Drosophila, which, in addition to representing an instance of the rarely observed invertebrate tumors, were of sex-linked hereditary character, and were lethal in the larval stage.

As the occurrence of tumors of certain organs has been quite definitely associated with functional relations in others, there would appear to be evidence that factors other than the simple mendelian characters advocated by Slye may play a part in their hereditary causation. Loeb in 1923 found that in mice ovarian function was distinctly related to the incidence of cancer of the breast, and that the advent of this tumor could be almost wholly averted by castration early in life. Obviously such a relation would imply the action of independent factors, any or all of which might have hereditary relationships, and so would complicate the rôle of heredity into a complex almost impossible of unravelment. That it was necessary to assume the existence of a multiplicity of factors in the explanation of the incidence of human cancer on hereditary grounds was the belief expressed in 1923 by Aebly, and again in 1928 by Warthin, who considered that in man there are at least four intrinsic factors, any one of which might be recessive or dominant. Further, somatic variations of nontransmissible character may determine the incidence of tumors, as has been observed in mice by Strong.

The relations of heredity to the occurrence of tumors are further complicated by the undoubted influence of chronic or other irritation in the causation of cancer. The probable interrelations between irritative and hereditary factors were summarized in 1923 by Loeb as follows: With H representing the element of heredity, S a cancerogenic stimulus and C the cancerous state itself, H plus $S \rightleftharpoons C$. Obviously, either element of the left side of the equation could conceivably, and apparently actually, reach the necessary intensity alone. Numerous instances may be found in the literature of experimental cancers that

appear to bear out this conception. Fibiger in 1916 found that different, but rather closely related, rodents reacted differently in regard to the causation of cancer by Spiroptera, which excited cancer readily in pied rats and only occasionally in white mice, even though the precursory lesions in the two animals were similar. Secher in 1920 found similar results in regard to oat-hair cancer, to which black rats were more resistant than other varieties. In regard to skin cancers caused by tarring, rats are notoriously almost absolutely immune, while mice are the most susceptible of the animals yet studied. With cysticercus sarcoma in rats, Curtis and Bullock found that there are marked familial differences in susceptibility. Slye observed in certain strains of her mice a marked tendency to the development of cancers at sites of local injury.

It may be questioned why, in view of the clear evidence of the importance of heredity in the incidence of spontaneous tumors in animals, there is so little indication of such relationship in the incidence of human cancers. A number of elements unquestionably contribute to the apparently largely negative character of human statistics. Even disregarding that emphasized by Wells—that of inaccuracy in the reports of human deaths [1]—it must be acknowledged that human data seldom extend over a sufficient number of generations to give an adequate conception of ancestral conditions. But even more important would appear to be the element stressed by Slye, the heterozygous character of human inheritance. Anything approaching the pure strains achieved by selective breeding of lower animals is of course impossible with man; and with the continuous and more or less enforced crossbreeding that has been exercised from time out of mind by human beings, it is only in exceptional circumstances that what there is reason to believe is an intricate hereditary effect can manifest itself openly as a distinctly familial incidence of cancer. But that such instances do occur the numerous cases cited in the literature show definitely.

CONDITIONS OF CANCEROUS GROWTH

In the development of a malignant tumor, there would appear to be a distinct possibility that two separable elements are concerned—first, the assumption by certain body cells of the property of unrestricted, malignant growth, and second, the existence within the body of conditions that permit their growth and survival. Although this second

1. In connection with these views of Wells, it is interesting to note that de Bovis, who in 1910 studied the statistical evidence of heredity in its relations to human cancer, found that while the data of Germany and Holland indicated that that might be a factor, this was not shown by Hungarian statistics—a difference which he ascribed solely to the unequal diagnostic accuracy in the respective countries.

element is purely a matter of surmise, it is a conjecture that essentially lies behind almost all attempts to cure cancer by other means than that of direct extirpation or other methods of direct destruction of the tumor.

To what extent, if any, does the knowledge of cancer gleaned from clinical or experimental evidence throw light on the actuality or the nature of this second element? Clinical evidence throws little, except the occasional observation that cancers progress more rapidly in relatively young and well nourished persons. As concerns the experimental study of cancer, such knowledge as has been afforded by it is derived mainly from observations on transplantable tumors, and its significance as applied to tumors of spontaneous development is of necessity open to some question.

Endocrine and Other Glandular Relations.—Sex Glands: Among the earlier attempts to influence the progress of malignant disease by the induction of a more or less general alteration of metabolism was the procedure, suggested and practiced by Beatson, of oöphorectomy in cases of mammary cancer, with or without thyroid medication. In a number of patients treated in this way Beatson reported amelioration or temporary regression of the carcinoma, but the effect does not appear to have been permanent. Similar results were reported by other, principally British, surgeons, as by Lett, who in 1905 stated that some 36 per cent of patients treated in this way showed improvement, and as late as 1909 Cahen reported favorable results after castration in younger patients with cancer of the breast. Numerous studies have been made on the effect of this operation on the progress of implanted tumors in animals, with results that on the whole must be regarded as conflicting or indecisive. In 1909 Graff reported that castration was without apparent effect on the transplantability of tumors. Goldzieher and Rosenthal in 1912, and Hilario in 1915, likewise failed to observe any effect of this operation with the transferable tumors of rats and mice, and Engel in 1922 found little evidence of action on the growth of transplanted tumors by the sex organs. Joannovicz in 1916 stated that while with transplanted sarcoma in mice castration was without apparent effect, with carcinoma there was slight, on the whole rather indecisive, evidence of restriction of growth. Almagia, Loeper, and Turpin and Zizine, likewise observed limitation of the growth of implanted mouse carcinoma in castrated animals. Findings with the same general tenor of growth restriction have been reported by Strong, who found that mice castrated before maturity become entirely resistant to the inoculation of sarcoma, and as to the influence of the ovary, Fornero found that in mice transplanted tumors grew more rapidly and with less necrosis if the mice had been treated by injection of the follicular fluid of non-pregnant mice, while the reverse effect was obtained by the injection of the follicular fluid of pregnancy. Murphy and Sturm also observed

that in mice of both sexes castration during the first 7 weeks of life led to increased resistance to tumor implantation, and that there was some, though less evident, increased resistance even when the operation was performed early in adult life.

Results diametrically opposed to these have been observed by Sweet, Corson-White and Saxon, who reported in 1913 that castration of male mice accelerated the progress of transplanted tumors and increased the probability of successful implantation. Korentschewsky in 1914 and 1920 published accounts of castration experiments on a number of animals; with a transplantable round cell sarcoma of the dog, there was an acceleration of tumor growth, and the reverse effect of retardation was observed in animals treated by injection of fresh testicular extract; with a rat sarcoma similar effects were observed, while castration alone had no apparent effect on the progress of implanted mouse carcinoma. As regards the female sex organ, he observed some inhibition of growth after the injection of corpus luteum or ovarian interstitial tissue. Goldzieher and Rosenthal, and Engel, in similar injection experiments, observed little effect after the administration of ovarian or testicular extracts, and Elsner saw little change with the latter. Other experiments in which enhanced growth was observed after castration were those of Asada on transplanted tumors in mice.

Adrenal Gland: Similarly uncertain results have followed interference with other endocrine glands. As regards the adrenal gland, Joannovicz found that resection of that gland increased the percentage of "takes" of carcinoma in mice, but reduced that of the "takes" of sarcoma. Auler, working with a rat sarcoma originally produced by inoculation of Bacillus tumefaciens, found that after unilateral adrenalectomy there was a period of enhancement of growth, followed by marked degeneration and necrosis, at times to complete recovery and at times with regression of the primary tumor, but with acceleration of metastases. Pearce and Van Allen found inhibition of the growth of a transplanted rabbit carcinoma after extensive, though incomplete, destruction of adrenal tissue, and Flörcken observed that delayed growth followed bilateral adrenalectomy in the mouse; unilateral excision had little effect. Roffo reported that adrenal decapsulation greatly inhibits tumor growth. With injected adrenal extracts, Goldzieher and Rosenthal failed to observe any effect on the progress of mouse tumors. Arloing, Jusserand and Charachon found that after the injection of extract of the adrenal of a rabbit that had been immunized to the tumor used in their experiments, there was some restriction of the growth of mouse cancer—a result that Woglom was unable to confirm. Sokoloff reported that the injection of adrenal extract and iron into transplanted tumors of rats and mice caused their regression. Recently Coffey and Humber advocated the treatment of patients with extracts

of adrenal cortex on the basis of apparently favorable results. Sugiura and Benedict, Itami, Sigemitsu and McDonald, and Bischoff and Maxwell, with animal tumors, have been unable to obtain results in any way confirmatory. Auler and Rubinow, however, with implanted tumors, have observed marked regression after the injection of a number of preparations of adrenal cortex. They would explain this by an alleged effect of the promotion of polysaccharide metabolism, perversion of which Auler considered as an important element of cancerous predisposition. Flack attempted to solve the problem of the possible influence of adrenal secretion on tumor growth by implanting inoculable sarcoma either into the adrenal or along with adrenal tissue into skeletal muscle. No effect was evident with the tumors implanted in the adrenal itself, but with the double implants there resulted inhibition, complete or partial, of growth of the tumor, an effect that was lacking in control experiments in which spleen, liver, thymus, corpus luteum or testis was substituted for the adrenal tissue.

Thyroid Gland: Stimulation of tumor growth after extirpation of the thyroid gland was reported by Korentschewsky in the case of a dog tumor, and by Van Allen and Pearce with their rabbit carcinoma. With mouse tumors Korentschewsky observed the opposite effect, though to an insignificant degree. Engel found evidence of a restriction of tumor growth by the thyroid gland; Honda reported that the administration of thyroid retarded the progress of rat sarcoma. No effect from the administration of various thyroid products could be detected by Elsner, Uhlenhuth and Woglom, nor by Goldzieher and Rosenthal from the use of thyrodin. Flack, using his method of implanting tumor tissue directly into the organ, or along with it in some remote site, found with rat sarcoma that the thyroid-parathyroid system would stimulate tumor growth, the effect being somewhat dependent on proximity. With extirpation of the gland there was delayed growth of the tumor tissue. In tissue cultures, Zakrewski observed that the presence of thyroid stimulated the growth of the Jensen sarcoma—an effect that was likewise manifested, though to a less degree, by the addition of sex and salivary glandular tissue, all from young animals, and by rat embryonic tissue. As regards the parathyroid alone, Goldzieher found that injection of the hormone of that organ showed very slight evidence of stimulation of the growth of mouse carcinoma.

Pituitary Gland: In the case of the pituitary gland, Robertson and Burnett in 1916 studied the action on tumor growth of various extractives from the anterior lobe. Among the substances extractable by alcohol, tethelin and entire extract were found to increase the growth of transplanted tumor, while lecithin caused retardation. Engel found evidence of stimulation by this gland, and Elsner got variable results depending on the preparation used. Seel found that in rabbits the

injection of pituitary extract had no effect on developed tar cancers, although it appeared to delay their onset. In these experiments, however, there was a complicating factor of marked nutritional disturbance. Morphologic studies of the changes in the pituitary gland that occur in malignant disease have been made by Rohdenburg and Bullock and by Karlefors. The former found none of specific character; Karlefors reported in cancerous individuals a reduction in the number of the eosinophils and an increase in that of the chief cells, but these changes were not specific and were apparently secondary. The negative findings of Rohdenburg and Bullock apply to the results of a general study of the ductless glands in cancer, as made by them.

Thymus Gland: Pearce and Van Allen found some evidence that removal of the thymus gland was followed by stimulation of implanted rabbit carcinoma, and Engel also was of the opinion that it exerted a growth-restraining effect. Korentschewsky reported that feeding of thymic tissue hindered the development of implanted mouse carcinoma. Hanson reported that the administration of thymus to patients with cancer was followed by amelioration. On the other hand, Bullock and Rohdenburg and Johnson could detect no effect by this organ on tumor growth, in experiments consisting of its excision in rats implanted with the Flexner-Jobling rat carcinoma, and Elsner saw no results from the injection of thymus extract into mice that had tumors. Magnini found that after removal of the organ there was restrained growth of a rat sarcoma, and Mischtschenko, that thymus tissue, with that of the spleen and the adrenal, promoted the earlier stages of the growth of implanted tumors.

Parotid Gland: An isolated observation by Grünbaum and Grünbaum to the effect that the parotid gland influences tumor growth, inasmuch as they observed in growing tumors marked degenerative changes after its excision, could not be confirmed by Levin and Sittenfield.

Lymphoid Tissue: The relations of the lymphoid and reticuloendothelial systems to cancerous growth have been the subject of repeated and extensive investigation. That lymphocytes play a large part in the so-called immunity to tumors was first suggested by the work of Wade on the infectious sarcomas of dogs, and for rat and mouse tumors by DaFano. Baeslack and Loeb and Harter also noted the importance of these cells in tumor defense, but that the action is one of protection against foreign tissue rather than against tumor as such was first indicated by the latter writers, who also recognized that this defense was not the sole one—a view that has been substantiated by the work of Mottram, Russ, and Russ, Chambers and Scott. Murphy and his co-workers, Hussey, Lieu, Maisin, Morton, Nakahara, Sturm and Taylor, in a series of experiments and reports principally on the effects of the x-rays on immunity to tumor, showed with some conclusiveness the important part taken by these cells in preventing

not only the growth of transferred tumors, but in general that of introduced foreign tissues. However, a number of more or less contradictory facts make the exact relationship of the lymphocyte to this defensive mechanism a matter of some uncertainty: The occurrence of lymphocytic accumulations within actively growing tumors, as found by Abetti, Woglom, and Loeper and Turpin; the recession of tumors without lymphocytic infiltration, observed by Bullock and Rohdenburg and, in the absence of lymphadenoid changes, by Woglom and Itami; the coexistence of tumor growth and a high blood content of lymphocytes, observed in the human being in lymphatic leukemia by Wood and in animals by Maeda and Wells; the growth of foreign tumors in close association with implanted splenic tissue in chick embryos, reported by Stevenson and Danchakoff—all indicate the complicated character of the relationships. The relation, however, would appear to be more particularly one of immunity to foreign tissue rather than to tumor growth, and its further discussion is not particularly pertinent here.

Spleen: Based largely on the fact that the spleen appears to possess a high immunity to the metastasis of malignant tumors, much experimental work has been devoted to the investigation of a possible rôle of this organ in tumor defense. In spite of the relative rarity with which metastases are found in the spleen, its freedom from involvement by tumor has been questioned particularly by von Hansemann, who reported a number of instances of its involvement. Kettle suggested that its relative immunity may be explained on purely mechanical grounds, as due principally to its contractile power.

It was shown rather early that the injection of splenic tissue, even from the same animal, could prevent the successful subsequent implantation of transplantable tumor (Woglom, 1910); but that this effect would appear to be one of rather general immunity to tissue transfer is indicated by the work of Rohdenburg, Bullock and Johnson, and Woglom himself, among others, who found that this effect is not peculiar to the spleen, but is shared by a number of other tissues and organs.

Implantation of tumor tissue into the spleen has yielded negative results, the implants growing there about as freely as at any other site, as found by Fränkl, Goldman, Levin, Oshima, and Roffo and Encina, although some evidence of resistance has been noted by Cimoroni, Brancati and Lazarus-Barlow and Parry. The simultaneous insertion of spleen and tumor, on the other hand, has appeared to yield some evidence of an immunity effect, as restriction of growth has been observed in these circumstances by Fränkl, Biach and Weltmann, Mottram and Russ, Donati and d'Agata, with a variety of animal tumors. Fränkl's results, however, would scarcely indicate any specificity for this effect, since he obtained similar results when the tumor

tissue was mixed with blood or with hepatic or renal tissue. The simultaneous but separate insertion of tumor and spleen, used as a control by a number of the experimenters cited, failed to show the inhibitory effect. With similar experiments, Oshima was not able to detect any evidence of restraint of growth by splenic tissue. Fischer and Lumsden studied the effects of splenic tissue on cultured tumor cells, with negative results.

Studies of tumor growth in splenectomized animals, as pointed out by Woglom, are complicated by the factor of the possibility of replacement of splenic function by other lymphadenoid tissues. Oser and Pribram believed that splenectomy increased the growth rate of transplanted tumors, and that the injection of splenic tissue had the opposite effect, and Lewin also observed what appeared to be occasional curative effects from the injection of splenic material derived from other tumor animals, to the greatest degree when the implantation had been intraperitoneal. Results in general similar to those of Oser and Pribram have been reported by Korentschewsky and were obtained also, though less constantly, by Joannovicz, who observed increased tumor growth after splenectomy in 2 animals, but the reverse in 1. Serafini, who damaged the spleen by vascular ligation, believed that in this condition there was accelerated tumor growth, but Simpson, after damage to the organ by severe exposure to the x-rays, could detect no direct relations between splenic damage and susceptibility to tumor. Mottram and Russ were unable to detect any effect from splenectomy on the course of implanted tumors in otherwise normal rats, but with immunized animals there were found microscopic evidences of a proliferation of the tumor cells, too slight to be grossly evident. Perrachia also observed what he believed to be evidence of antiplastic activity on the part of the spleen, and Brüda reported that tumor tissues grow in vitro more intensively when the plasma used is taken from splenectomized animals. Bauer found that injected extracts of spleen have the effect of raising the surface tension of the serum, and believed that the tumor-inhibiting action of the organ rests in this feature. As regards more particularly the effect of splenectomy, in contrast to the foregoing results that would indicate antiplastic power, a considerable list of workers—Bullock and Johnson, Bullock and Rohdenburg, Dobrovoskaia-Zavadskaia and Samssonow, Donati, Morris, Oshima, Pearce and Van Allen, Woglom and Zeitlin—have been quite unable to detect any effects on the growth of tumors from splenic extirpation.

The frequency of enlargement of the spleen in tumor-bearing animals, especially in rats and mice, has been cited as evidence of specific relations between the organ and the tumor; but as Woglom points out in his general discussion of these phases of the cancer problem, this is too inconstant to be of evidential value, and is more

probably to be explained by concomitant or antecedent pathologic features, especially in the case of mice.

Reticulo-Endothelial System: The reticulo-endothelial system has been implicated more particularly in the causation of cancer by Erdmann, who observed that after blockage by injections of india ink it was possible to induce tumors of the Flexner-Jobling type in rats by means of apparently cell-free filtrates of that tumor; but some of her unprepared control animals also showed similar tumors, so that the exact effect of the blockage is questionable. Büngeler observed after similar blockage in mice the appearance of inoculation tumors after the injection of tumor cells damaged by chloroform beyond the point at which they would grow in more natural circumstances, and Lignac and Kreuzwendedich von dem Borne noted increased susceptibility to both mouse sarcoma and carcinoma in similar circumstances, as did Urban and Schnitzler. On the other hand, Theilhaber reported that in cases of human cancer improvement followed the blockage of the reticulo-endothelial system, and the isamine-blue therapy practiced by Roosen would appear to depend for its effect largely on the affinity of that material for reticulo-endothelial tissue. Psaromitas observed no effect from reticulo-endothelial blockage on the progress of transplantable tumor in the mouse, but in the fowl the Rous sarcoma was considerably restricted in its development by this procedure. Munck, working with mouse carcinoma, observed that there resulted from reticulo-endothelial blockage an inhibitory effect of transitory character, which disappeared after 16 days.

Diet.—Suggestions that dietary conditions might be in part responsible for an apparent increase in the incidence of human cancer are not infrequent in the earlier literature of that disease, although these seldom include any explanation of the manner of the supposed action. Williams, in 1896, was responsible for such a suggestion, and Sawyer in 1900, and both implied that the increased ingestion of meat was the responsible factor. In 1902 Williams, finding from statistical evidence that while cancer was relatively rare in the Jews of London, that people in the United States did not appear to enjoy a similar immunity, sought the explanation of this difference in the matter of dietary adequacy. McReddie, discussing in that year the occurrence of cancer in India from the same point of view, argued that its frequence there was not in evident contradiction to the alleged association of cancer with a meat dietary, since the population of that country is not as decidedly vegetarian as is usually assumed; but he was able to find no apparent relationship there between the prevalence of cancer and meat consumption. Needless to say, any great importance that may be attached to a flesh dietary largely vanishes when it is recognized that cancer is frequent in herbivorous

animals, and the interest now lies in the possible relationships of a general dietary to the occurrence of malignant disease—a possibility somewhat indirectly reflected in the article of Jacobson that appeared in 1907, in which he suggested that cancer might represent the result of diversion of excess energy from normal activities to unrestrained proliferation of tissue, and by the observations of Robertson and Ray that cancer is most likely to occur in mice with a relatively energetic growth rate, with a lead so obtained that usually persists for life.

Protein: The study of the behavior of the transmissible tumors of animals in relation to modifications of diet, even though accepted with the reservations that must attach to all study of tumors essentially foreign to their new host, affords some information in the line of present interest—the effects of modification of the individual on the progress of already established tumors. Indicative of the effects of general nutritional inadequacy on the growth of tumors are the experiments of Corson-White, Rous and Sugiura and Benedict, all of whom found that in the earlier stages an ample supply of food was essential to the progress of implanted tumors. As regards modification of the intake of protein, its results do not appear to be very considerable. Sweet, Corson-White and Saxon found that with a diet in which the protein elements were entirely of vegetable origin, the percentage of successful inoculations of tumor in mice was reduced to about one sixth of the normal proportion, and in a later article they believed that they could vary the susceptibility of animals by dietary alterations that affected thyroid activity, anything which tended to stimulate that organ increasing the probability of successful implantation, while thyroid-depressant substances decreased the number of "takes." Rous, using the same modifications as those of Sweet, found that while with some tumors the restraining action was manifest even with tumors of considerable size, with others the effect was evident only if the underfeeding was begun before the growth of the tumors was well established. Some influence was exerted even on spontaneous tumors, to the extent that the restricted dietary would usually delay their recurrence after partial excision, as well as the appearance of metastases, a restraint that persisted only during the period of dietary restriction. That the effects of protein modification were more probably those of insufficiency rather than character appears from the work of Marsh, who found that mice on a vegetable diet containing an unusually wide range of protein substances were not affected as regards their susceptibility to implantation, and by Sugiura and Benedict, who found that the character of the protein material in the diet of rats and mice did not appreciably affect the growth rate of transplanted tumors, provided that such material was present to above 8 per cent of the food intake. Drummond found that while a diet low in protein would cause some retardation of

tumor growth in rats, this in general was associated with more general evidence of malnutrition in the form of severe loss of body weight. Apparently the requirements as pertains to amino-acids are just about the same as for general bodily welfare, since restriction of tumor growth occurred with deficiency of some of these, especially tryptophan, and restriction of the diamino-acids to the point of general inadequacy likewise retarded tumor growth.

Fats and Lipoids: As regards fat and lipoids, Robertson and Burnett, studying the effect of a milk diet on transplanted tumors in rats, found that with these animals there was some reduction in percentage of "takes," an effect which they ascribed to deficiency in cholesterol, particularly as they found that the injection of that substance accelerated the growth of implanted tumors, while lecithin had the opposite effect. The latter effect Bennett could not confirm, but Robertson and Ray, in a later paper, confirmed the earlier findings, although they were not evident in the case of spontaneous tumors, possibly because of the considerably shorter life of the animals. Moravek observed a similar accelerative effect from cholesterol with sarcomas, but not with mouse carcinoma. He found a depressant action of lecithin, evident with carcinoma even when administered along with small amounts of cholesterol—an effect which he ascribed to alteration of cellular permeability. Rondoni reported the observation of excessive tumor growth after the administration of cholesterol, and the opposite effect with lecithin, and Corson-White found that a high cholesterol content in the diet of tumor-bearing rats favored the onset of metastases. Bernstein and Elias found that the addition of either cholesterol or lecithin to the diet of tumor-bearing animals enhanced the growth of the tumors. Addition of an abundant supply of fat to the diet would appear to increase tumor growth; Beebe found this effect on the addition of butter, and Akematsu with lanolin.

Entirely unrelated to the action of lipoidal material through nutrition or through a presumably more or less direct effect on the cancer cells themselves is the action of certain materials of this general class on so-called immunity to tumor. Nakahara found that the injection of oleic acid or other unsaturated fatty acids or their salts, if this precedes by about ten days the implantation of tumors, serves to protect the animals so treated from the tumors. This effect he found was indirect and achieved through its effect on the lymphocytic reaction, and it appears to be similar to that observed by Lewin and Brancati, of immunity produced by the injection of nucleic acid. With olive oil, Nakahara observed an almost directly reversed effect, namely, the obliteration of the immunity to implantation of tumor which had been produced by the injection of homologous blood; this effect of reversion of potential immunity he also ascribed to modification of the lymphocytic reaction.

Carbohydrate: Van Ness, Van Alstyne and Beebe found that a deficiency of the carbohydrate fraction of the diet of animals into which tumors had been implanted was of little effect, unless it was begun at least several weeks before the implantation, but in that case there was marked restriction of progress of the tumors. Benedict and Lewis likewise found the carbohydrate content of the diet of great importance in determining the progress of tumors—rat sarcoma—and found that the administration of phlorhizin to tumor-bearing animals caused rapid disintegration of the tumors. From the addition of lactose to the diets of rats and mice with implanted tumors, Woglom was unable to detect any effect on the progress of the tumors, but apparently the dietary was already adequate before the addition. Händel and Tadenuma found with rats that an unbalanced diet with excess of carbohydrate favored tumor growth, an effect that was slightly accentuated by the injection of insulin, but they were unable to detect any change after the injection of phlorhizin. Goldfeder likewise found that abundance of carbohydrate favored tumor growth; however, with what would appear to be a greatly unbalanced diet with great excess of carbohydrate and insufficiency of other elements—an exclusively banana diet—Sugiura and Benedict found great restriction of the growth of the Flexner-Jobling rat tumor. The general effect of the carbohydrates in forwarding the growth of tumors does not appear to be entirely a matter of facilitating the growth of established tumors, as Rondoni found that the parenteral introduction of dextrose accelerates the action of tar on rabbits during the precancerous stages.

Vitamins: Joannovicz, and Fränkl and Fürer in confirmation, found that diets with a general deficiency of vitamins led to marked restriction of tumor growth, as did Ludwig. Such an effect was not observed by Kretzschmar nor by Thies, nor by Benedict and Rahe, although in the experiments of the latter observers the animals were given sufficient vitamin B in the form of yeast to preserve their health. As concerns the various vitamins specially, vitamin A is regarded by Burrows as more or less identical with his hypothetic growth-restraining ergusia. Caspari and Ottensooser found that restoration of vitamin A to a vitamin-free diet enhanced tumor growth, but only in the presence of an adequate supply of vitamin B. Erdmann, in studying the development of spontaneous tumors in circumstances of vitamin deficiency, found that this was more likely to occur with absence of this vitamin and abundance of vitamin B. Drummond was unable to observe any restriction of tumor growth in rats on a diet deficient in vitamin A. With vitamin B, a more definite rôle would appear to have been established. The experiments of Erdmann, which are corroborative of Burrow's identification of this vitamin with his growth-promoting substance, archusia, have just been referred to. Drummond had found that while implanted tumors would grow for a time in animals on a diet

free from this vitamin, the growth would cease with the exhaustion of the animal's store of it. Funk failed to detect much effect from variation of this in the diet of fowls with the Rous sarcoma, but Heymann and Gallinek found that its absence greatly reduced the incidence of successful implantation of tumor in the rat. Caspari and Ottensooser, in a comprehensive survey of the work along this line, both as conducted by themselves and others, concluded that of the vitamins, B is the single one absolutely essential to tumor growth, even though absence of others may be of influence indirectly, as in the case of vitamin A or in that of vitamin D, the addition of which to the diet they found could enhance the growth rate of implanted tumors. As concerns vitamin C, Centanni found that with an exceptionally transplantable tumor of mice, if the animals were placed on a diet with especial restriction of this along with nuclein and phosphorus compounds as long as 10 days before implantation, there was a complete abolition of "takes," and that with already established tumors there was arrest and complete absorption if the growth had not gone too far.

Mineral Salts: In the case of mineral salts, principal attention has been devoted to the relations between potassium and calcium compounds and tumor growth. Beebe found in 1904 that there was a disturbance in the normal proportions of these salts, with a relative excess of potassium over calcium, in the case of rapidly growing tumors. Goldzieher in 1912 reported that in tumor-bearing mice treated by injection of salts of potassium or of calcium, there was, in the case of the former, an increase of tumor growth to about 48 per cent above that in the control animals, and in the case of the latter a reduction of 37 per cent. Sugiura, Noyes and Falk found in 1921 that immersion of the Flexner-Jobling rat tumor in solutions of calcium salts greatly inhibited its future growth, an observation that was confirmed in the following year by Troisier and Wolf, who observed the reverse effect with the use of potassium salts, and again by Goldfeder in 1928. The restraining effect on tumor growth of magnesium or its salts, reported by Reding with developing tar cancers, could not be confirmed by Itami for transplanted tumors. As regards the tumor-promoting action of potassium salts, Langfeldt observed that diets deficient in this metal hinder to a great degree the progress of transplanted tumors.

Gaseous Metabolism: Efforts to interfere with the development of tumors by interference with the general gaseous metabolism of the body have been made principally by Fischer, Buch Anderson, Demuth and Laser, and by Fischer-Wasels. All of their experiments were designed to promote oxidative metabolism, with the idea of suppressing anoxybiotic cleavage of dextrose, which Warburg found to be the predominant feature of tumor metabolism. In the experiments reported by the former group of observers, mice with implanted tumors were

kept in an atmosphere of oxygen under increased tension. A certain degree of healing of the tumors was observed in these circumstances, best when to the effect of the altered gas relations there was added that of injection of copper and selenium salts. Fischer-Wasels reported that even more striking results have followed the use of mixed oxygen and carbon dioxide, again with the added effect of injected colloidal iron preparations, or with that of injected dextrose and insulin. He reported that cancerous patients with such treatment show not only evidence of a restraint of the growth of the tumors but general improvement, as well. To what extent these results are to be explained by the theory on which the experiments were based, to what extent they were due to more general metabolic relations, is obscured by the findings of Campbell and Cramer to the effect that implanted tumors in mice and rats showed greatly diminished rates of growth when the animals were kept over long intervals under diminished oxygen tension, and by Woglom's finding that the progress of implanted tumors was not appreciably affected by induced acidosis or alkalosis. That the growth of a tumor is sensitive to general conditions of the body has been indicated by Mandl and Singer, who found that toxins due to fatigue favored the growth of implanted tumors in mice, as well as by the relations shown between pregnancy and the progress of the tumor—relations that appear to be inconstant. Von Graff found that with certain exceptions the growth of transplanted tumors was slower during periods of pregnancy, a finding confirmed by Slye. Mischtschenko found in rats with implanted tumors a retardation of neoplastic growth during pregnancy, while during lactation the tumors showed accelerated progress. Krotkina, on the other hand, with tar tumors in mice, observed accelerated growth during pregnancy.

Summary.—The more significant observations of the relations between tumor growth and conditions of the host would appear to be outstandingly the dependence of the former, at least in its earlier stages, on a general adequate nutritive supply, with special reference to that of carbohydrate and probably of fatty or lipoidal material. Endocrine disturbance has not shown any very definite relationships to the progress of malignant tumors. Of the vitamins, aside from indirect effects that would appear to be associated with more general nutritive disturbance, vitamin B would appear to have direct relationships to tumor growth. As regards relations of cancerous growth to mineral elements, the evidence of the action of potassium salts in facilitating, and of calcium salts in restraining, such growth, appear to be firmly established.

Correspondence

THE INTERNATIONAL ASSOCIATION FOR GEOGRAPHIC PATHOLOGY

To the Editor.—A note concerning the organization of this Association has already appeared in the ARCHIVES (**9**:711, 1930). During 1930 and 1931 the national committees in various countries cooperated in a survey on the geographic distribution, racial variations and anatomic, physiologic and etiologic features of hepatic cirrhosis. The results of these surveys, submitted by each national committee were assigned for review and summary under five subdivisions, as follows: (1) Pathologic Anatomy of the Liver in Hepatic Cirrhosis, de Josselin de Jong, Utrecht; (2) Pathologic Anatomy of Other Organs in Hepatic Cirrhosis, R. Roessle, Berlin; (3) Clinical Features and Manifestations, Noel Fiessinger, Paris; (4) Etiologic Factors and Experimental Production of Cirrhosis, W. E. Gye, London; (5) Disturbances of Metabolism in Cirrhosis, F. C. Mann and J. L. Bollman, Rochester, Minn.

The presentation and discussion of these reports constituted the program for the first conference of the Association, held at Geneva, Oct. 8 to 10, 1931. No member of the committee for the United States was able to attend the conference. The assembled representatives agreed that the form known as Laennec's cirrhosis should be understood to include not only the granular contracted liver, with ascites, splenic enlargement and circulatory disturbance, but also a form of enlarged liver the fundamental histology of which is not essentially different. This obviates the confusion existing between Hanot's cirrhosis and this hypertrophic form of Laennec's cirrhosis. They recognized the existence of various intermediate stages or degrees of cirrhosis. The evidence that copper is an important factor in cirrhosis in man was not deemed sufficiently convincing. On the other hand, alcohol was considered the one known important factor, whether acting alone or in combination with infectious agents as suggested by evidence presented by workers in the United States.

The organization of the association in permanent form was an important feature. The provisory committee, which had voluntarily conducted the activities of the association, was replaced by a permanent executive committee of five members, one of whom is to be designated from the United States. The second conference was set for the autumn of 1934. The place of meeting and the subject for the next survey will be determined by the executive committee and will be announced later. Unfinished results and discussions concerning cirrhosis were deferred for consideration at the next conference.

Membership in the Association is open to those interested in this branch of medical science. One may become a member on recommendation of a member of the national committee of his country and the payment of the annual fee of 5 francs (Swiss).

There is a sentiment, in which the members of the Committee for the United States share, that the method of the first survey was perhaps too statistical. It is the hope of many that, as the organization develops, its scope and activities may be somewhat modified and that it will enlist the interest and cooperation of eminent workers in other divisions of medical science as well.

The official transactions will be published by Kundig, Geneva. These will include the five reports as given and the by-laws of the association.

V. H. MOON, M.D.,
Chairman of the Committee for the United States,
Jefferson Medical College, Philadelphia.

Notes and News

University News, Promotions, Resignations, Appointments, etc.—Sydney C. Dalrymple has been appointed instructor in pathology in Tufts College Medical School, Boston.

Antonio Dionisi, professor of pathologic anatomy in the University of Rome and well known for his researches on the etiology of malaria, died suddenly while addressing a congress on rheumatism.

A. Murray Drennan, professor of pathology in Queen's University, Belfast, has been appointed professor of pathology in the University of Edinburgh.

Coroner's Office in San Francisco Becomes Appointive.—According to the new charter of San Francisco, which has just gone into effect, the office of coroner is taken out of the elective group and placed in the appointive group, the present incumbent of the office becoming a life time appointee on good behavior.

Professorship of Legal Medicine in Harvard Medical School.—George Burgess Magrath, medical examiner in Boston, has been appointed professor of legal medicine in the Harvard Medical School. The professorship was established by a gift by Mrs. Frances Glessner Lee, Littleton, N. H. This appears to be the first endowed professorship of its kind in this country.

Award of Gerhard Medal.—The Gerhard Medal of the Philadelphia Pathological Society has been awarded to Alfred N. Richards, professor of pharmacology in the University of Pennsylvania, for his experimental investigations of renal function.

Abstracts from Current Literature

Experimental Pathology and Pathologic Physiology

THE CARDIODYNAMIC EFFECTS OF ACUTE EXPERIMENTAL MITRAL STENOSIS. L. N. KATZ and M. L. SIEGEL, Am. Heart J. **6**:672, 1931.

A ligature method was developed to produce stenosis of the mitral orifice with a minimum of artefacts due to traction and with no interference with the coronary supply to the ventricle. The cardiodynamic changes were studied in dogs by optical manometers recording on bromide paper. The importance of recognizing, minimizing and evaluating the effects of artefacts is emphasized. Experimental stenosis of the mitral orifice produced the following immediate changes: a variable amount of slowing of the heart rate in most cases; a marked abbreviation of the ejection and total systole time in both ventricles; an elevation in the pressure of the left auricle; an increase in the magnitude of the left auricular contraction; a decrease in the maximum pressure developed by the left ventricle; a variable change in the level of the initial pressure of the left ventricle (due to an unavoidable artefact); a fall in systolic, diastolic and pulse pressure in the aorta; a variable change in the pulmonary arterial and right ventricular pressures — the pressure sometimes fell, sometimes rose or remained unchanged; the occasional appearance of presystolic oscillations on the left ventricular pressure curve; a steeper gradient of pressure rise during diastasis in the left ventricular pressure curve. These changes are in part the direct result of the stenosis, causing impediment of flow to the left ventricle and "damming back" of fluid in the pulmonary circuit. In part, they depend on the decrease in coronary flow resulting from the fall in arterial blood pressure. Compensatory mechanisms soon tend to restore conditions toward normal. Evidence is given which suggests that these compensatory mechanisms include: an increase in the pressure head of the left auricle, an increase in the magnitude of auricular activity, a prolongation of the time for diastolic filling and an augmentation of the aspirating action of the left ventricle as evidenced by the steeper rise of the diastolic portion of its pressure curve. All these factors tend to overcome the impediment of the obstruction, thereby augmenting left ventricular filling and lessening the damming up of blood in the pulmonary circuit.

AUTHORS' SUMMARY.

THE EFFECTS OF CERTAIN SUBSTANCES ON THE CILIATED EPITHELIUM OF THE GUINEA PIG. D. R. A. WHARTON, Am. J. Hyg. **14**:109, 1931.

Bacterial poisons, light and certain other factors were found to inhibit ciliary movement in the tracheal epithelium of the guinea-pig, whereas bacterial toxins and venom failed to have any demonstrable effect. The inhibitory factors of the bacterial cultures (poisons) are considered to be of protein origin. Observations of the effect of antigen on the ciliated epithelium of sensitized guinea-pigs and on ciliated epithelium treated with precipitating antiserums failed to elicit any change in the action of the cilia which might be used as a criterion of hypersensitiveness or immunity. The cilia were inhibited in different periods of time by various sputums, and it is suggested that the sputum in certain respiratory conditions, as bronchitis, may affect the movement of cilia adversely. The examination at autopsy of preparations from various parts of the respiratory tract may give valuable information as to the condition of the ciliated epithelium. Because of the simplicity of the technic, a great deal more attention should be given to ciliary function and the factors affecting it, by the use of preparations of ciliated epithelium from warm-blooded animals. The results obtained are more logically applicable to conditions in man than those obtained by using molluscs, protozoa or even frogs, and the further study of the subject should broaden ideas on the defensive mechanisms of the respiratory tract.

AUTHOR'S SUMMARY.

PRIMARY HYPOCHROMIC ANEMIA (ERYTHRO-NORMOBLASTIC ANEMIA). WILLIAM DAMESHEK, Am. J. M. Sc. **182**:520, 1931.

Seven cases of anemia are described, in which, although the symptomatology was that of pernicious anemia, the hematologic findings were those of "secondary anemia." Specimens taken from the sternal bone marrow for biopsy in three cases disclosed marked hyperplasia due to crowding with erythroblasts and normoblasts. The relationship of this anemia to the megaloblastic hyperchromic anemia called "pernicious" is discussed in detail. The possibility that the cases described are instances of chlorosis is discussed and rejected.

EXTRACTS FROM AUTHOR'S SUMMARY.

IDIOPATHIC HYPOCHROMEMIA. EDWARD S. MILLS, Am. J. M. Sc. **182**:554, 1931.

Evidence for considering idiopathic hypochromic anemia or hypochromemia as a disease entity is presented, and twenty-three cases of the disease are reported. The disease is confined to the female and runs a very chronic course with symptoms common to any moderately severe anemia. The important clinical features are an absence or a great diminution of free hydrochloric acid in the gastric contents, an absence of etiologic factors, a hypochromic blood picture and a tendency to resist ordinary forms of therapy for anemia. Twenty-one of twenty-three patients have been treated successfully with a capsule containing ferrous carbonate and copper carbonate U. S. P. Many of these cases had proved refractory to the iron alone before the iron-copper therapy was begun.

AUTHOR'S SUMMARY.

REGENERATIVE POSSIBILITIES OF THE CENTRAL NERVOUS SYSTEM. R. W. GERARD and R. R. GRINKER, Arch. Neurol. & Psychiat. **26**:469, 1931.

In a series of experiments on new-born rats and on fetuses in utero, the spinal cords were transected by a single clean cut with a cataract knife, and subsequently studied histologically, the "clinical" course of the animals being carefully observed during the interim. Many experiments yielded negative or no results because the animals died or the spinal column became displaced, etc. Several rats operated on at birth, however, gave evidence of a gradual return of function. One animal, studied with special care, which showed evidence of a complete section at the time of operation, was entirely paralyzed and anesthetic below the lesion for two weeks, while in a subsequent three weeks the recovery of sensation and voluntary motion was practically complete. The spinal cord of this animal showed no evidence of a lesion. Several rats operated on in utero were born from five days to a week later with the sense of pain, voluntary motion or both present in the hind quarters. The spinal cords showed partial lesions or none at all. We cannot decide on the correct interpretation of these cases. The possibility of the growth of nerve fibers into and across a lesion after a complete or partial transection is definitely established. The immature spinal cord also possesses remarkable powers of physiologic reorganization which may lead to full return of function below an almost complete separation of the cord. A consideration of the evidence bearing on regeneration in the mammalian central nervous system from other sources as well as from our own results indicates that although some growth of nerve fibers from the cut end of axons may appear, return of function due to anatomic regeneration has not been proved.

AUTHORS' SUMMARY.

INJURY AND REPAIR WITHIN THE SYMPATHETIC NERVOUS SYSTEM. S. S. TOWER and C. P. RICHTER, Arch. Neurol. & Psychiat. **26**:485, 1931.

The preganglionic sympathetic nerve fibers were cut on the right side before entry into the stellate ganglion in a series of twenty-six adult cats. Until the completion of regeneration and for from two to six weeks thereafter, records were taken of the skin-resistance of the fore paws and of the galvanic skin response.

Observations on sweating were also made. The effects of operation were: the immediate elimination of the spontaneous waves in skin potential and of the galvanic skin response; an immediate increase in skin-resistance. The resistance of the skin reached a peak many times the maximum normal figure between the second and fifth days after operation, and thereafter fell slowly and with fluctuation. Between the third and seventh weeks, as skin-resistance again approached a normal figure, the action currents of the skin reappeared. This reappearance was taken as the time of reconstitution of the connection between the central nervous system and the periphery. It averaged twenty-eight days. Evidence of some form of function of the synapse is noted several weeks before this date. The observations on sweating made at the same time indicate that the galvanic skin response is a far more delicate test for the presence of sympathetic innervation than gross observation of the activity of the sweat glands.

AUTHORS' SUMMARY.

THE NEURO-ANATOMY IN RESPIRATORY FAILURE. KNOX H. FINLEY, Arch. Neurol. & Psychiat. **26**:754, 1931.

A careful anatomic study of two cases of poliomyelitis in which respiratory troubles were the prominent features led to the conclusion that the respiratory center is not represented by a definite group of cells in the medulla, but that several levels of the central nervous system are involved. The neural mechanism of respiration is thus integrative. One such level is in the reticular formation of the brain, which in Finley's cases was destroyed by foci of softening.

GEORGE B. HASSIN.

ACUTE EXPERIMENTAL GLOMERULITIS FOLLOWING REPEATED INJECTIONS OF HAEMOLYTIC STREPTOCOCCI INTO THE RENAL ARTERY. F. D. W. LUKENS, Bull. Johns Hopkins Hosp. **49**:312, 1931.

A diffuse glomerulitis and interstitial inflammatory reaction could be obtained in the kidney of the rabbit by the repeated injection, at weekly intervals, of killed hemolytic streptococci into the left renal artery. This reaction was not observed after the first or after the second injection, but occurred in all of three rabbits four days after the third injection. It is suggested that the reaction is analogous to the Arthus phenomenon, which occurs under these conditions within an organ.

AUTHOR'S SUMMARY.

HYPERVITAMINOSIS. E. J. KING and G. E. HALL, Canad. M. A. J. **25**:535, 1931.

The administration of massive doses of viosterol to chickens produced a condition of anorexia, loss of weight, extreme emaciation and finally death. Hypercalcemia resulted, and on histologic examination heavy deposits of calcium were observed in the secretory tubules of the kidneys. Histologic examination of the femurs showed the matrix of the trabeculae to be normal, but suggested a low amount of calcareous deposit within it. The percentage of ash, calcium and phosphorus of the bones, however, was normal. The bone phosphatase appeared to be present in less than the normal amount. The daily administration of parathormone appeared to produce no ill effects in chickens, comparable to those produced by viosterol. Histologic examination of the femurs showed productive fibrosis of the bony trabeculae without evident deposition of lime salts in the hyperplastic tissue. The mineral constituents and the phosphatase of the bone were present in normal amount.

AUTHORS' SUMMARY.

THE PERMEABILITY OF THE CUTANEOUS VENULES AND ITS FUNCTIONAL SIGNIFICANCE. F. SMITH and P. ROUS, J. Exper. Med. **54**:499, 1931.

The permeability of the venules of the skin of the mouse greatly exceeds that of the capillaries. A mounting gradient of permeability exists along the further

portion of the latter. The significance of these facts is discussed with relation to conditions in human skin. The cutaneous venules are differentiated for several functions besides those ordinarily attributed to them, and must be considered as specialized organs.

AUTHORS' SUMMARY.

THE BONE MARROW IN FASTED AND POLYNEURITIC PIGEONS. R. A. MOORE and O. W. BARLOW, J. Exper. Med. **54**:761, 1931.

The histologic changes of the bone marrow in pigeons deprived of food and in pigeons with rice disease are essentially the same. The histologic changes of the bone marrow in pure vitamin B deficiency consist of degeneration, edema and slight endothelial proliferation of the small vascular channels, but with active hematopoiesis. The anemia of rice disease in pigeons is in large part a starvation anemia and is not directly related to vitamin B deficiency.

AUTHORS' SUMMARY.

THE EFFECTS OF UNILATERAL NEPHRECTOMY ON OPEN GLOMERULI AND URINE OUTPUT. R. A. MOORE and W. W. SUMMERVILLE, J. Exper. Med. **54**:767, 1931.

Renal shock with oliguria or anuria after a unilateral operation on the kidneys was not produced in seventeen rabbits. For a period of two hours after unilateral nephrectomy, the one kidney carried on a proportionate part of the work of the previous two kidneys, and there was no evidence of functional compensation. There was a general correlation between the open glomeruli and the output of urine.

AUTHORS' SUMMARY.

THE CHOLESTEROL FUNCTION OF THE GALLBLADDER. R. ELMAN and J. B. TAUSSIG, J. Exper. Med. **54**:775, 1931.

Cholesterol determinations of gallbladder and hepatic bile obtained from the same source reveal a greater concentration in the former, even after the inspissating effect of the gallbladder is allowed for. This evidence, together with that from other experiments, indicates that the gallbladder has the power to excrete cholesterol into its lumen. There is evidence also that infection may accelerate this excretion. An hypothesis is presented to explain the precipitation of cholesterol in the bile, and the bearing of these findings on the pathogenesis of cholesterol stones is briefly discussed.

AUTHORS' SUMMARY.

THE GONAD-STIMULATING SUBSTANCES OF THE ANTERIOR LOBE OF THE PITUITARY BODY AND OF PREGNANCY-URINE. ZONJA WALLEN-LAWRENCE and H. B. VAN DYKE, J. Pharmacol. & Exper. Therap. **43**:93, 1931.

The assay of gonad-stimulating principles (hebin) by the use of immature male and female rats is discussed. The method used is based on the weight of the seminal vesicles in the male, and the ovaries in the female. The preparation of a crude pituitary hebin from various sources is discussed. It is pointed out that while beef anterior lobes are a poor source for this substance, good yields can be obtained from sheep and pork pituitary bodies. Pituitary hebin, administered subcutaneously, can initiate estrus in the hypophysectomized rat. Associated with estrus, there occur follicular maturation and uterine changes. Crude pituitary hebin does not dialyze through collodion or parchment; it is heat stabile (99 C.). It may be extracted from pituitary bodies at both acid and alkaline p_H. Hebin from pregnancy urine does not dialyze through collodion or parchment; it deteriorates when boiled in aqueous solution. Urinary hebin stimulates the testis and ovary with equal facility; pituitary hebin, on the other hand, stimulates the ovary in a much smaller dose than that having a moderate effect on the testis.

AUTHORS' SUMMARY.

RAYNAUD'S DISEASE: WITH SPECIAL REFERENCE TO ARTERIOLAR DEFECTS AND TO SCLERODERMA. THOMAS LEWIS and E. M. LANDIS, Heart **15**:329, 1931.

There is a form of diffuse scleroderma in which those portions of the skin that are exposed are most affected; sclerodactyly and discoloration of the fingers on exposure to cold are the rule. The vascular defect underlying discoloration of the fingers in this disease is of the same nature as that occurring in Raynaud's disease of the usual type. Evidence is collected, which shows that in cases of severe Raynaud's disease (with or without diffuse scleroderma) the vessels to the fingers are altered structurally. The circulatory manifestations of Raynaud's disease are due to a local vascular defect. In milder forms this defect is expressed as a susceptibility to enter a state of spasm; in the severer forms, spasm is reinforced by local structural change.

AUTHORS' SUMMARY.

EXPERIMENTAL DIFFUSE HEPATITIS. GUY ALBOT, Ann. d'anat. path. **8**:437, 1931.

Inflammation provoked by toxic substances is associated with early, parenchymatous, cellular lesions. The hepatic lobule functions from the periphery toward the center in pathologic conditions as it does normally. In the course of diffuse experimental hepatitis, it is possible to distinguish an initial periportal stage, a stage of tubular hyperergy and of reticulosis and finally a stage of "asymmetry" ("asymetrie lesionelle," an expression coined by Noël Fiessinger to show that at this period the lesion is less schematic than in the early stages). The acute, subacute and chronic varieties of diffuse hepatitis depend on the toxic properties and the dose of the drug, on the mode of its administration and also on the resistance of the animal. Acute diffuse hepatitis shows an atrophic centrolobular degeneration, which resembles acute yellow atrophy. The processes of experimental acute hepatitis are invariably the same although provoked by different agents. They always go through the same initial stages, showing elementary inflammation of the hepatic lobule. There is but one type of a diffuse inflammatory process in the liver. Cases differ, however, by their evolution, showing multiple aspects from an acute atrophic hepatitis to a cirrhosis. Experimental data go hand in hand with the observations made on human beings.

B. M. FRIED.

EXPERIMENTAL VASCULAR SCLEROSIS IN THE KIDNEYS OF RABBITS. N. GOORMAGHTIGH, Ann. d'anat. path. **8**:585, 1931.

Chronic arterial hypertension obtained through enervation of the carotid sinus and section of the aortic depressive nerves causes a progressive hyalinization of the glomeruli. This is marked about three and one-half months after operation in instances in which the arterial pressure is maintained above 15 mm. It is accompanied by a slight interstitial sclerosis, which is particularly marked in the neighborhood of the glomeruli, and also by slight atrophic changes in some segments of the uriniferous tubules. Experimental, chronic, arterial hypertension also results in hyperplastic and degenerative lesions of the renal arterioles. The vascular and the glomerular lesions of the kidney are secondary to the arterial hypertension. The kidney is sensitive to prolonged variations in the arterial pressure, and the glomerular tufts are more sensitive than the afferent arteriole. The author also observed that rabbits with vascular sclerosis of the kidney showed a hyperplasia of the parathyroids.

B. M. FRIED.

SOME EFFECTS OF ROENTGEN RADIATION ON DIVIDING CELLS IN TISSUE CULTURES. H. W. LOVE, Arch. f. exper. Zellforsch. **11**:435, 1931.

The radiosensitivity of a cell is a function of its displacement from maturity. If the backward displacement in time of a cell from maturity, that is, the state of the cell just preceding the division process, is less than about 180 minutes, its

radiosensitivity is constant and independent of the displacement. If the backward displacement in time of a cell from maturity is greater than about 180 minutes, there is a decrease in its radiosensitivity. The reduction in the number of dividing cells in an irradiated tissue culture is due to an inhibition of some fracton of the cells that normally would have entered mitosis during the process of irradiation. The temporary increase in the mitotic count of an irradiated culture after four hours' incubation is due to the superimposition of a complete or almost complete recovery of temporarily inhibited cells on an increased survival (due to decreased radiosensitivity) in the cell groups displaced from maturity to the extent of about three hours at the commencement of the experiment.

AUTHOR'S CONCLUSIONS [WILHELM C. HUEPER].

BIOLOGIC EXPERIMENTS WITH OVARIAN THYROID MATERIAL. A. PLAUT, Klin. Wchnschr. **10**:1803, 1931.

Iodine containing material from ovarian thyroid tissue gave positive results in experiments with acetonitril on rats and mice, as well as in repeated feeding experiments on tapoles.

Pathologic Anatomy

CORONARY THROMBOSIS IN AN INFANT AGED FOUR MONTHS. ROBERT EWART RAMSAY and R. M. CRUMRINE, Am. J. Dis. Child. **42**:107, 1931.

Autopsy on an infant, aged 4 months and 8 days, disclosed thrombosis of the descending branch of the left coronary artery. The original lesion of the coronary artery appeared to be of an infectious nature, and was probably a bacterial embolus. In a search of the literature on coronary thrombosis, no report of the occurrence of this condition in so young a child was found.

FROM AUTHORS' SUMMARY.

NIEMANN-PICK'S DISEASE (ESSENTIAL LIPOID HISTIOCYTOSIS). H. G. PONCHER, Am. J. Dis. Child. **42**: 77, 1931; B. WASCOWITZ, Am. J. Dis. Child. **42**:356, 1931.

Poncher describes a case in a Jewish boy, aged 18 months, and Wascowitz one in a Jewish girl, 7 months old, and both give the observations at autopsy. The association of amaurotic family idiocy (Tay-Sachs' disease) and Niemann-Pick's disease is discussed.

PAUL MERRELL.

AORTIC ANEURYSM RUPTURING INTO THE CONUS ARTERIOSUS OF THE RIGHT VENTRICLE. E. H. SCHWAB and C. B. SANDERS, Am. J. M. Sc. **182**:208, 1931.

A case of acquired aneurysm of the ascending aorta with rupture into the conus arteriosus of the right ventricle is reported. The resulting physical signs simulate closely those of congenital heart disease. The two previously reported cases are briefly reviewed.

AUTHORS' SUMMARY.

CEREBRAL ANEURYSM AND CORTICAL HERNIATION. J. J. KEEGAN and A. E. BENNETT, Arch. Neurol. & Psychiat. **26**:36, 1931.

Cerebral aneurysm should be suspected in cases of spontaneous subarachnoid hemorrhage, particularly in persons under 40 years of age. Anatomic peculiarities of the cerebral arteries and infectious emboli are significant in the etiology of cerebral aneurysm. Arteriosclerosis and syphilis rarely are the cause. Focal neurologic signs frequently indicate the location of the aneurysm after rupture, rarely before, unilateral oculomotor palsy being the commonest localizing sign in

this series. Ligation of the internal carotid artery on the side of the lesion is indicated if recurrent hemorrhage occurs. Cortical herniation into arachnoid granulations is of common occurrence in conditions with intracranial pressure. An unusual case of thrombosis of the motor cortex from herniation into large pacchionian bodies is reported.

AUTHORS' SUMMARY.

CEREBRAL BIRTH PALSY. LEON FREEDOM, Arch. Neurol. & Psychiat. **26**: 524, 1931.

Study of a feebleminded girl, aged 19, with signs of pyramidal and extrapyramidal nerve lesions and epileptic attacks in whom the course of the disease was progressive, revealed avascular areas in the parietal, occipital and temporal regions of the cortex. The involved portions of the cortex were either degenerated or showed proliferation of Hortega cells and new formation of capillaries. Many areas appeared normal. The smaller blood vessels showed endarteritis. In some areas of the temporal lobe, only a few cells in the outer cortical layers remained. Equally severe were the lesions in the corpus striatum, where the small ganglion cells were more involved than the large elements, and where avascular areas were also in evidence. The pallidum was even more involved, and some portions were entirely devoid of ganglion cells. Glia rosets were present in the optic thalamus, while the frontal lobe and the cerebellum, except the nucleus dentatus, were practically intact. The process was mainly degenerative. The thyroid gland showed a decreased amount of the colloid substance and hyperplasia of the connective tissue, with a diffuse small round cell infiltration of the entire gland substance. Freedom sums up the changes as degenerative, involving mainly the cortex and much less the basal ganglions and the nucleus dentatus. Clinically it was a case of infantile cerebral palsy, but anatomically it could not be classified.

GEORGE B. HASSIN.

DUODENAL ATRESIA. F. BATINI, Pathologica **23**:232, 193

In an instance of congenital duodenal atresia, a discontinuity of the mucous membrane alone was the cause.

E. HAAM.

GAMNA'S AREAS IN SYPHILITIC SPLEEN. G. PATRASSI, Pathologica **23**:266, 1931.

Siderous splenogranulomas (Gamna's areas) were found in great numbers in the spleen of a 5 year old child with congenital syphilis, and in the spleen of a 61 year old woman with numerous sclerogummatous lesions.

E. HAAM.

MULTIPLE DIVERTICULA OF THE SMALL INTESTINE. G. GIANNOMI, Pathologica **23**:277, 1931.

Thirty-six diverticula of different sizes and shapes were found in a piece of small intestine, 96 cm. long. The author explains the etiology on the basis of senile atrophy of the muscularis.

E. HAAM.

RELATION OF LYMPHOCYTES, MONOCYTES AND HISTIOCYTES TO EACH OTHER. G. SEEMANN, Beitr. z. path. Anat. u. z. allg. Path. **85**:303, 1930.

For his contribution to the controversial problem of the interrelationships of lymphocytes, monocytes and histiocytes, Seemann used chiefly the rat, because of the relatively high percentage of monocytes in the blood of this animal. Mice, rabbits, guinea-pigs and material from slaughtered domestic animals were also used. The work was done in Aschoff's laboratory. For the differentiation of the cells under consideration, chief reliance was placed on the method of supravital staining by neutral red and janus green. Smears and sections were also stained by the eosin-azure II and the oxidase method. The criteria accepted for the differ-

entiation of the cell types in supravitally stained preparations are those laid down by Sabin and her co-workers. Seemann proposes the name monocytoid for the cell of the blood and peritoneal and other fluids that has a nucleus like that of the typical monocyte but, instead of the characteristic neutral red roset of the latter, several relatively large clumps of coarser and finer neutral red granules and vacuoles. It is this type of cell, according to Seemann, that Maximow and his pupils have interpreted as a hypertrophied lymphocyte, through which are unfolded the multiple potencies ascribed to the lymphocyte by Maximow. The monocytoid cell, in the opinion of Seemann, is not a hypertrophied lymphocyte in transition to a monocyte, polyblast or other type of cell. It has no relationships to the lymphocyte, but has relationships to the monocyte and has the same origin as the latter. The monocytoid and monocytic cells are derived from an ubiquitous indifferent mesenchyme cell, and constitute, with the lymphocyte and the granulocyte, a distinct third leukocytic form. Having left the blood stream, the monocytes and monocytoid cells are transformed into histiocytes. The histiocytes of an inflammatory area therefore have a double origin, coming in part from emigrated monocytes and monocytoid cells, and in part from slumbering tissue histiocytes. Fibrocytes and capillary endothelia cannot be transformed into histiocytes. The reticulo-endothelia of Aschoff are closely related to the histiocytes. In lymph nodes in which an aseptic inflammatory reaction was induced, in tissue cultures of lymphoid tissues and in incubated blood and peritoneal fluid, Seeman could detect only regressive changes in the lymphocytes, and he believes that the occurrence of progressive and developmental changes in these cells still remains to be established.

O. T. SCHULTZ.

UNMASKING FRAGMENTATIO MYOCARDII. O. TAMURA, Centralbl. f. allg. Path. u. path. Anat. **52**:1, 1931.

After studies of fresh press preparations and serial and ordinary sections, the author concludes that the picture called fragmentation of the myocardium is an artefact due to folds in the muscle tissue. These folds are caused by atonic muscle fibers, which appear in contrast to the intact fibers. The name "plicoformatio myocardii" is suggested in place of the older term.

GEORGE RUKSTINAT.

LINGUAL STRUMA AND HYPOTHYREOSIS. P. HEILMANN, Centralbl. f. allg. Path. u. path. Anat. **52**:129, 1931.

A walnut-sized lingual mass of thyroid gland tissue was found in a 39 year old woman who died of pulmonary embolism following hysterectomy. No evidence of a thyroid gland was found in the usual location, although parathyroid bodies were noted. The superior and inferior thyroid gland arteries had normal origins, and the disposition of the external carotid and thyrocervical trunks was normal. The lingual thyroid tissue had alterations characteristic of a nodose struma. The position of the tumor just back of the foramen cecum seemed to point to a lack of descensus of the thyroid gland, which then remained small and hypoplastic and eventually formed a tumor. An analogy is drawn between the probable course of events in this case and that observed in undescended testes by Erdheim. As concerns the other glands of internal secretion, no thymic tissue was found; there were: small cystic structures in the intermediate zone of the hypophysis, but no disturbances of the cell relationships elsewhere; small fibrous ovaries, and nodules of cortical tissue of the suprarenal glands.

GEORGE RUKSTINAT.

URETER BIFIDUS CAUDALIS. S. SALTYKOW, Centralbl. f. allg. Path. u. path. Anat. **52**:177, 1931.

This rare condition was found in a woman, aged 60, who died shortly after a radical operation for sarcoma of the uterus. The accessory ureteral mouths were seen on cystoscopic examination, but were difficult to find post mortem.

The anomalous ureters were confined to the wall of the urinary bladder; the right was 4 cm. long, the left 2 mm. long, and both opened about 0.5 cm. above the main ureters. The natural ureteral orifices were only 1.2 cm. apart.

GEORGE RUKSTINAT.

THE CUTANEOUS CHANGES CAUSED BY THALLIUM ACETATE. J. VON VÁSÁRHELYI, Dermat. Wchnschr. **92**:649, 1931.

Histologic study during and after complete epilation in young white rats given thallium acetate showed a low grade inflammatory process with infiltration of the hair follicles by polymorphonuclear leukocytes. Chemical tests revealed thallium in the skin. The author concludes that epilation by means of thallium is due to its direct action on the skin and that its excretion by the cutaneous glands results in inflammation, leading to loss of hair.

LAWRENCE PARSONS.

FATAL PULMONARY EMBOLISM. F. KAZDA and W. STOEHR, Deutsche Ztschr. f. Chir. **231**:187, 1931.

The article contains an analysis of 145 patients who had been operated on and 152 patients with internal diseases who showed at autopsy occlusion either of the trunk or of one principal branch of the pulmonary artery. These instances were observed in 29,132 autopsies. The material is divided, for comparison, into two groups, the first embracing the period during the Great War (1915 to 1918) and the second the time between 1922 and 1928.

Postoperative Embolism.—The number of postoperative fatal embolisms decreased during the war, increased considerably in the period from 1922 to 1927, and decreased again slightly in 1928. Most of the fatal postoperative embolisms occurred in the months of December and March. There were many more women than men who died from postoperative pulmonary embolism, especially in the period after the war. Most of the persons concerned were from 50 to 60 years old; no postoperative fatal embolism occurred in childhood.

The greatest danger of embolism seems to be between the sixth and ninth days after surgical intervention, but the condition can occur even two or three weeks after operation. In the period from 1922 to 1928, not only was the frequency of embolism but also the size of the thrombotic masses increased. As the source of the embolism, thrombi were found as a rule in the veins of the right leg. Abdominal, especially gynecological, operations carry the greatest danger of embolism. Only one case was observed following resection of a goiter. The most frequent concomitant conditions were organic heart disease and vascular disease as well as pathologic changes in the kidneys, pleura and bronchi, less often in the liver and the bile ducts, and, in more than one third of the cases, in the spleen. General adiposity was present in one sixth of the surgical cases.

Embolism in Patients with Internal Diseases.—The fatal pulmonary embolisms in patients with internal diseases also showed a definite increase during the postwar period. They were more frequent in April, October and November than in other months. There were three times as many women as men in this series, and the majority of the patients were older than 60 years. The original thrombi were found as a rule in the veins of the right leg. In one third of the material, the principal disease consisted in organic changes of the heart and blood vessels, less often in those of the central nervous system. Diseases of the respiratory and digestive tracts followed in frequency. As concomitant diseases, changes in the respiratory tract were observed most frequently (more than two thirds of the cases). In more than one half of the cases there were organic changes in the liver and bile ducts, and in 50 per cent of the cases there were organic diseases of the heart and blood vessels. In more than 50 per cent, pathologic conditions were noticed in the urinary tract. General adiposity was present in one eighth of the medical material.

Etiologic Considerations.—The decrease in frequency of postoperative fatal embolism during the war and the increase in fatal postoperative embolisms and in those in patients with internal diseases in the years after the war indicate that the change in the nutrition during these different periods may have been responsible. The relative frequency of embolisms in adipose persons seems to point to the same factor. As contributing causes are suspected the less strict indications for surgical intervention during recent years and the longer duration of life due to more effective treatment of patients with internal diseases. There does not seem to be any evidence that epidemics of influenza played a rôle. The prevalence of women, especially of those in the menopause, suggests that postclimacteric changes of the female organism favor the development of thrombosis.

The almost complete absence of embolism after operations for goiter and the significance of the menopause are in favor of the assumption that internal secretion plays an important rôle in the etiology of thrombosis. The frequent coincidence of adiposity and embolism and, on the other hand, the occurrence of embolism in families suggest a certain relationship between constitution and embolism.

C. A. HELLWIG.

APLASTIC ANEMIA. H. ROSCH and G. HOLLAND, Folia haemat. **44**:48, 1931.

The authors discriminate between cryptogenic or a "virtual aplastic anemia" (described in the German literature as "hemorrhagic aleukia") and anemia with an aplastic blood picture. In the first, the bone marrow is primarily involved, while in the second, although the marrow is more or less affected, the disturbance is rather functional. They report one example of the virtual type with an unknown etiology. The second case was one which was thought to result from hemorrhoidal bleeding, but which was traced to benzene poisoning. In the third case, an isolated intestinal tuberculosis complicated anemia with an aplastic blood picture.

B. M. FRIED.

LYMPHOGRANULOMATOSIS OF THE BONES. R. DRESSER, Strahlentherapie **41**:401, 1931.

Twenty cases of lymphogranulomatosis of the bones are described. About 10 per cent of all cases of lymphogranulomatosis show involvement of the bones. The changes produced resemble, on roentgenologic examination, those caused by cancerous lesions. They are usually destructive, but a productive variety also occurs. The spine, pelvic bones, skull and sternum are most frequently involved.

WILHELM C. HUEPER.

TISSUE CULTURE: ITS SIGNIFICANCE FOR PATHOLOGIC ANATOMY. G. HERZOG, Verhandl. d. deutsch. path. Gesellsch. **26**:9, 1931.

While Roux was the first to study the development of explanted organs of the chick embryo in vitro, the modern practical method of tissue culture is entirely the work of American investigators (Harrison, Carrel, Burrow, L. Loeb, M. and W. Lewis). The new method has furnished important data on the microscopic structure of cells. The mitochondria are regarded as normal constituents of the protoplasm, and there is no transformation of mitochondria into pigment granules, fat drops or vacuoles. The melanin is formed—as A. Fischer demonstrated in cultures of embryonal iris and retinal epithelium—in finest granules, independently of the nucleus or the mitochondria. The duration of a mitotic division averages in vitro about from twenty-five to thirty minutes. Liquefaction of the culture medium is observed in different degrees and under various conditions. It is especially marked in cultures of normal mucous cells and in those of most malignant tumor cells.

Fibroblasts can be obtained from almost all organs of the embryonal and the adult organism. They form not only from the fibroblasts proper, but also from

endothelial cells, reticulum cells, periosteum and perichondrium, embryonal connective tissue and heart muscle. In the cultures of fibroblasts, all transitions between cell adhesions and syncytial arrangements may be observed, a fact that does not disprove the doctrine of the cell as the biologic unit, since also in the syncytial formations of the tissue culture the single cell territories seem to be preserved.

The macrophages play the next most important rôle in cultures of mesenchymal tissue. They are derived from the so-called histiocytes (reticulo-endothelial cells of Aschoff), adventitial cells, large mononuclear wandering cells and large monocytes of the circulating blood. These cell forms survive in vitro only a certain time; some of them are transformed into fibroblasts. A transformation of fibroblasts into macrophages, on the other hand, can be demonstrated in pure cultures only under special conditions.

The growth of epithelial cells in vitro is not always, as generally believed, less pronounced than that of fibroblasts. All epithelial cells have as a rule a tendency to form membranes. The growth of the cell carpet is due not only to cell division, but also to a harmonic ameboid movement of the cells.

The problem of cell differentiation was studied by Herzog and Schopper on different mesenchymal organs of guinea-pigs. When the culture medium was poor in embryonal extract, the development of argyrophil and later of collagen fibers was noted. Abundant provision of embryonal extract, on the other hand, interfered with the differentiation.

In most tissue cultures, a large central area of the explanted tissue fragment undergoes necrobiosis. Only a peripheral zone survives, and from there the proliferating cells migrate into the culture medium. In cultures of the spleen or of the lymph glands, small lymphocytes and leukocytes migrate into the medium immediately, followed about fifteen hours later by the so-called macrophages, while the fibroblasts do not migrate before the second or third day.

The behavior of blood vessels was studied in tissue cultures of the omentum. In the first hours there is a migration of adventitial cells. While the endothelial elements first show proliferation, soon progressive dissolution of the capillaries takes place. From the second or third day on, the endothelial cells migrate into the medium, and large portions of the capillaries disappear. From artery stumps, straight, often long, buds grow out and unite into a network as in the living organism. In later stages, however, the endothelial cells proliferate diffusely and cannot be distinguished from cultures of fibroblasts. Schopper observed even the forming of argyrophil and collagen fibers in cultures of endothelial cells.

The spleen is the most frequently cultivated organ. There is wide dissension of opinion regarding the behavior of the lymphocytes. Most of those that migrate in the first hours die. The proliferating lymphocytes of the peripheral zone are larger and take vital stain. Not every small lymphocyte can change into a large macrophage. Also in cultures of lymph nodes, most of the small, immediately migrating lymphocytes die. Maximow, using lymph nodes of the rabbit, to which he added extract of bone marrow, demonstrated the development of granulocytes from ungranulated cells.

Carrel and Ebeling obtained pure cultures of monocytes from leukocytes, and Maximow traced the development of argyrophil fibers to blood cells. But Herzog is of the opinion that fibroblasts originate only from the so-called monocytes or histiocytes of Aschoff.

When tubercle bacilli are added to tissue cultures, a specific proliferation of epithelioid and giant cells is noted, which have phagocytic properties. In cultures of blood cells, tubercle bacilli cause the formation of epithelioid cells, a fact that suggests the possible hematogenous origin of epithelioid cells in the living organism. From the observation that in some tissue cultures bacilli containing fibroblasts are found, the inference may be drawn that the formation of collagen fibers in tubercles is due to the fibrillogenic potency of epithelioid cells.

The proliferation of epithelial cells in vitro resembles that in the body during regeneration or organization. Pure cultures of epithelial cells can be regarded

as permanent regenerative states. Often the culture of epithelial cells resembles the atypical proliferation in the body, but a transformation of normal epithelial cells into true carcinoma has never been accomplished in vitro.

The superficial cells of serous membranes grow first in epithelium-like fashion, forming continuous carpets, and liquefy the plasma, but in latter passages they proliferate like fibroblasts, and there is no liquefaction of the medium noted. Schopper demonstrated the development of argyrophil fibers between proliferating serosa cells, thus the epithelial and mesenchymal properties of serosa cells are well illustrated in tissue cultures.

From the morphologic point of view, the tumors of animals have been thoroughly investigated, while the cultivation of human new growths is still rudimentary.

Cancer cells grow in vitro, like normal epithelial cells, forming membranes. By adding fibroblasts, the formation of solid strands and tubules and cornification are favored. The time of mitotic division does not seem to differ in normal and malignant cells; the incidence of mitotic figures is, according to A. Fischer, much higher in cultures of carcinoma. The number of chromosomes is smaller in the cells of mouse carcinoma than in normal cells, and the form and size of the chromosomes vary considerably.

Herzog concludes from this review that growth and histogenesis in tissue culture follow the same principles as in the living organism.

C. A. HELLWIG.

Microbiology and Parasitology

DISSOCIATION OF DIPHTHERIA BACILLUS. M. E. MAVER, J. Infect. Dis. **49**:9, 1931.

Variants of the diphtheria bacillus are described as they appeared in a study of the growth and the production of toxin of this bacillus in synthetic mediums. The dissociation seemed to progress in gradual stages to the more attenuated coccoid form. The yellow and pink pigmentation of pellicles and colonies in attenuated cultures was observed, as well as all variants described by others. The antigenic relationships between the variants and the original Park 8T strain indicate a closer relationship between the rods and the rodlike forms and the original strain than between the coccoid forms and the original strain. The fermentation reactions of the variants differed from those of the original strain in some cases. Of thirty-one freshly isolated strains of diphtheria bacilli grown on synthetic agar, ten showed dissociation into coccoids after the first transfer and fifteen after the second. The use of synthetic medium on which the diphtheria bacillus can become adapted to growth and production of toxin is recommended for the study of the dissociation of this micro-organism.

AUTHOR'S SUMMARY.

DISTRIBUTION OF DIPHTHERIA BACTERIOPHAGE. G. H. SMITH and ELIZABETH F. JORDAN, Yale J. Biol. & Med. **3**:423, 1931.

Phage for Bacillus diphtheriae has been obtained from sewage; from the throat washings, stools and urine of patients with diphtheria (in one instance ten days after the organism had disappeared from the throat); from carriers; from the throats of persons who were not carriers, or from whom the so-called diphtheroid forms could not be recovered by ordinary cultural methods; from the air and from the floor sweepings of laboratories in which work with diphtheria bacteriophage was being conducted, and from 100 per cent of all field cultures of diphtheria bacilli subjected to examination. The significance of this wide dissemination of diphtheria bacteriophage cannot be determined. Whether or not it represents an exceptionally delicate index of contamination pointing to a wider distribution of diphtheria bacilli or of forms allied to them remains unsolved. The relationship, if any exists

between diphtheria bacteriophage and diphtheritic infection, is likewise unknown. Possibly some of the conflicting reports of the spontaneous appearance of bacteriophage may be explained by the demonstration that the bacteriophage corpuscle or the lytic principle adherent to particulate matter may be recovered from the air and from dust.

CATAPHORESIS EXPERIMENTS WITH TYPHUS VIRUS. I. J. KLIGLER and L. OLITZKI, Brit. J. Exper. Path. **12**:69, 1931.

Experiments are reported bearing on the electric charge of the virus of typhus and the possibility of recovery of the virus by cataphoresis from tissues of immune animals. The results of the experiments show that the virus wanders to the positive pole. This may signify either that the virus carries a negative charge or that this is carried by the associated proteins. It has not been possible by cataphoresis to obtain the virus from tissues of animals that had recovered from typhus infection. It has not been possible to separate the virus from virus-antiserum mixtures by cataphoresis of suspensions of p_H 6 and 8.6, respectively. So far as recovery of the virus from tissues of immune animals is concerned, the virus of typhus differs from the filtrable viruses studied by Olitsky and his associates.

AUTHORS' SUMMARY.

THE EFFECT OF THE X AND V GROWTH-FACTORS ON THE PATHOGENICITY OF INDOL-PRODUCING STRAINS OF INFLUENZA BACILLI. A. B. ROSHER, Brit. J. Exper. Path. **12**:133, 1931.

The experiments described indicate that the pathogenic action of a microbe that does not produce any notable quantity of toxic substance in vitro can be disclosed more readily by introducing with it its necessary growth factors. The healthy peritoneal cavity does not contain the necessary factors, and therefore influenza bacilli will not grow therein. If, however, these factors are supplied either by injury to the tissues as a result of the injection or by including them in the inoculum, growth can take place, and toxic substances may then be produced under conditions more favorable to their preservation than in a test tube. The application of this principle to the influeza bacillus shows that 71 per cent of indol-producing strains are pathogenic in mice, whereas those that produce no indol are practically nonpathogenic.

AUTHOR'S SUMMARY.

STUDIES ON PROTEIN-FREE SUSPENSIONS OF VIRUSES. I. J. KIGLER, L. OLITZKI and M. ASCHNER, Brit. J. Exper. Path. **12**:178, 1931.

Cataphoresis experiments with protein-containing and protein-free suspensions of a Bacillus coli phage and fowl-pox virus indicate that the results heretofore reported have been influenced by the protein. The charge measured was therefore chiefly that of the protein to which the virus was adsorbed. On the basis of the results in protein-free suspensions, it appears that both the B. coli phage and the fowl-pox virus are sensitive to acid reactions, and carry positive or negative charges according to the reactions of the medium. The phage is amphoteric in acid and decidedly alkaline solutions, and chiefly negatively charged in neutral and mildly alkaline solutions. The fowl-pox virus is positively charged on the acid side, is amphoteric in neutral solutions, and carries a negative charge in alkaline solutions.

AUTHORS' SUMMARY.

THREE CASES OF PSITTACOSIS WITH TWO DEATHS. H. R. FISHER and R. J. HELSBY, Brit. M. J. **1**:887, 1931.

Psittacosis is still liable to occur in this country, and should be borne in mind when one or more patients in a household are suffering from an influenzal type of illness, with early signs in the lungs and perhaps some typhoid-like symptoms,

such as epistaxis, abdominal distention, vomiting, constipation or diarrhea. Especially should such a diagnosis suggest itself if influenza is not prevalent in the neighborhood. Parrots are not the only birds that cause psittacosis in man. In the report of the Ministry of Health (Reports on Public Health and Medical Subjects, no. 61, London, H. M. Stationery Office) lovebirds, thrushes and canaries, among other birds, are stated to have been the cause of human illness. It is not certain how many types of birds suffer from diseases communicable to man, so the fact that a patient keeps birds should arouse suspicion in doubtful cases of human illness. All bird-keepers should take care always to wash their hands after attending to the birds, and especially before taking food. An unusual factor in the cases described in this article is that three generations of human psittacosis followed from the original sick budgerigar. Cosman, quoted in the Ministry's report, mentioned a woman who caught psittacosis from a patient whom she nursed and afterward infected her own child, but such a sequence is sufficiently unusual to be worth noting. The infection of a trained nurse in the course of her duties shows the care required in dealing with psittacosis, and incidentally, therefore, the necessity of early diagnosis of the disease. The nurses attending these patients were warned to treat them like patients with typhoid, and this is probably all that can be done. So far as is known, this is the first instance in this country of the infection of a hospital nurse with psittacosis by her patient, and, even so, two of the three nurses in attendance escaped the disease.

AUTHORS' SUMMARY.

MICROBIC DISSOCIATION OF B C G. R. S. BEGBIE, Edinburgh M. J. **38**:174, 1931.

Dissociation of B C G into rough, smooth and intermediate colonial types is found. Although the evidence of virulence is not clearcut, the smooth type is the most virulent, the rough type intermediate in virulence and the intermediate type least virulent. The smooth type is described as moist and shining, with a central raised dome. The intermediate colony has an umbilicated center with an irregular, narrow fringe, which does not spread. The rough type is composed of heaped up coils without a fringe, and has a waxy appearance.

EDNA DELVES.

ACTION OF ACETONE EXTRACTS OF TUBERCLE BACILLI. B. IAKHNIS and S. CHAGALOVA, Ann. Inst. Pasteur **46**:579, 1931.

Subcutaneous inoculations of acetone extractives of tubercle bacilli favored the development of lesions in guinea-pigs previously inoculated with the filtrable elements of tubercle bacilli. After six or seven injections, the site of inoculation of the filtrate usually showed caseous or noncaseous ganglions containing the organisms. The invasive capacity of isolated organisms seemed to be greater the longer the course of the injections of the extract and, correspondingly, the more marked were the caseous nodes from which the organisms were recovered. This invasive capacity seemed in several ways to correlate with the pathogenesis as influenced by acetone extract. The activity of the extract appeared specific. Diagnostic application is suggested, with the use of serial injections of extract in animals receiving pathologic material potentially containing the tuberculous "ultravirus."

M. S. MARSHALL.

THE DIAGNOSIS OF TUBERCULOSIS IN MONKEYS. A. NOHLEN and M. SARVAN, Beitr. z. Klin. d. Tuberk. **77**:186, 1931.

The usual tuberculin tests are unreliable in monkeys. Following the intramuscular injection of from 3 to 5 cc. of a mixture of ophthalmotuberculin and old tuberculin, tuberculous monkeys die within from one to three days. The same injection has no effect on nontuberculous monkeys.

MAX PINNER.

THE SIGNIFICANCE OF DOSE IN REACTION TO TUBERCLE BACILLI. E. SANTO, Beitr. z. Klin. d. Tuberk. **77**:191, 1931.

Different amounts of bacilli injected into the cornea produce different degrees of tissue reactions, but the quality of the histologic picture is always the same. The same observation was made on subcutaneous injections into guinea-pigs. The regional lymph nodes, however, show always, regardless of the amount of bacilli, maximal reactions. The quality of the tissue reaction, both locally and in the regional lymph nodes, was not effected by dosage. By counting the tubercle bacilli in foci of human pulmonary tuberculosis it was found that the quality of the histologic picture was independent of the number of bacilli.

MAX PINNER.

AGRANULOCYTOSIS. W. HUEBER, Frankfurt. Ztschr. f. Path. **40**:312, 1930.

Hueber believes that agranulocytosis is not a disease per se, but a complex of symptoms in certain cases of infectious diseases. The term "agranulocytic septicemia" seems more appropriate. The disease occurs mainly in women, but is also encountered in the other sex. It is not found more frequently during puberty or during the climacterium as was suggested by some authors. A generalized bacterial infection seems the important etiologic moment. Such infection might be detected either by the history of the case and the clinical course, or by a bacteriologic, anatomic or histologic examination. There are no grounds for the belief that a specific inflammation may give the clinical picture of agranulocytosis. Either increased virulence or chronic action of bacteria might be responsible for such a condition. It is probable that the toxins in such cases produce paralysis of the bone marrow.

O. SAPHIR.

SPIROCHETES IN THE EYE FOLLOWING SUBSCROTAL INOCULATION OF SYPHILIS. KEIHO KAMADA, Klin. Wchnschr. **10**:1116, 1931.

The corneal tissues in five of ten syphilitic rabbits contained spirochetes when examined at varying intervals after scrotal inoculation. Spirochetes were not found in the lens and vitreous chamber.

AUTHOR'S SUMMARY.

BACTERIAL COUNTS IN ARTERIAL AND VENOUS BLOOD IN ENDOCARDITIS LENTA. ERICH ZDANSKY, Ztschr. f. d. ges. exper. Med. **76**:571, 1931.

Bacterial counts were made in ten cases of endocarditis lenta, the blood being taken from the brachial artery and from a vein of the elbow. Of nineteen positive cultures, nine showed a distinctly higher count in blood taken from the artery, nine very little difference in count, and one a distinctly higher count in blood from the vein.

PEARL ZEEK.

FILTRABLE FORMS OF THE TUBERCLE BACILLUS. G. W. SCHMIDT, Ztschr. f. Hyg. u. Infektionskr. **112**:95, 1931.

A great number of experiments and a large number of guinea-pigs used in them gave no evidence for the existence of a particular pathogenic, filtrable, invisible form of the tubercle bacillus. The positive results of other authors are questioned. Old tuberculin from commercial and other sources contained large quantities of dead organisms, which were unaltered in form and acid-fast staining.

EDNA DELVES.

TUBERCULOSIS OF PLEURAL LYMPH NODES. R. ROOTS, Ztschr. f. Tuberk. **60**: 125, 1931.

In 200 necropsies on patients who had not died of pulmonary tuberculosis, the pleural lymph nodes were examined. All patients were 35 years or older. In

46 of these, little nodules were found in or immediately below the pleura. In some cases, multiple nodules, a total of 147, were found. On microscopic examination, 36 of the 147 foci were not lymph nodes and did not show tuberculosis. One hundred of them were pleural lymph nodes. Seventeen of these lymph nodes showed insignificant changes, such as anthracosis and fibrosis. Eight of these lymph nodes showed hyaline nodular scars, which did not show anything characteristic of tuberculosis. But these nodes that came from 7 different patients are the only lesions that could possibly have been caused by tuberculosis. These findings are totally different from those reported by Anders and Schmöe. It is concluded that pleural lymph nodes are not infected hematogenously, but directly from the pulmonary tissue.

MAX PINNER.

METAL SALT THERAPY IN EXPERIMENTAL TUBERCULOSIS OF GUINEA-PIGS. L. E. WALBUM, Ztschr. f. Tuberk. **60**:204, 1931.

Guinea-pigs were infected with virulent bovine bacilli which killed controls within seventy-nine days with generalized tuberculosis. Twenty animals were treated, ten receiving cadmium chloride and ten manganese chloride. Treatment was started fifteen days after the infection, when the animals had palpable enlargement of the lymph nodes. The manganese salt was used in concentrations of from 10^{-5} to 10^{-10} molar, and the cadmium in a concentration of from 10^{-7} to 10^{-11} molar. About half of the guinea-pigs treated did not show any sign of tuberculosis at autopsy, which was never performed earlier than three months after the infection.

MAX PINNER.

ISOLATION OF TUBERCLE BACILLI FROM THE BLOOD OF TUBERCULOUS PATIENTS. K. JONTOFSOHN, Ztschr. f. Tuberk. **61**:35, 1931.

An attempt was made to isolate tubercle bacilli from the blood of forty-one patients with pulmonary tuberculosis and nine patients with surgical tuberculosis. Löwenstein's recent method was used. Only in three cases of pulmonary tuberculosis was it possible to demonstrate the presence of tubercle bacilli in the blood.

MAX PINNER.

PATHOLOGIC ANATOMY OF UNDULANT FEVER. F. GREGERSEN and T. M. LUND, Hospitalstid. **74**:349, 1931.

In undulant fever there may be enlargement of the spleen, with congestion and hyperplasia of the pulp, but shrinking of the follicles; foci of granulation tissue in the spleen, liver and other organs; also parenchymatous degeneration.

Immunology

IMMUNOLOGICAL STUDIES OF COLDS AND INFLUENZA. G. HOWARD BAILEY, JANET M. BOURN and V. A. VAN VOLKENBURGH, Am. J. Hyg. **14**:453, 1931.

The case discussed presents the following interesting features: (1) a natural respiratory infection which, from bacteriologic and serologic evidence, was presumably a true primary infection with Hemophilus influenzae; (2) an illness which did not resemble true influenza in that it was afebrile, lacked prostration, requiring confinement in bed, and was comparatively mild in its effect; (3) leukocytosis during the acute stage of the illness; (4) cultures from the pharynx and tonsillar fossae that were positive for H. influenzae at least twelve weeks after the onset of the illness, prior and subsequent cultures having been consistently negative; (5) serologic evidence (by means of complement-fixation tests prior to and following the illness) of a definite increase in the antibody content of the blood against

homologous and heterologous strains of H. influenzae, evident three weeks after the onset of the illness, greatest at the end of seven weeks and approaching the level observed prior to the illness during the succeeding weeks; (6) as determined by the maximum titer, one homologous strain of H. influenzae (1522) that appeared to be the most specific in antibody response.

FROM AUTHORS' SUMMARY.

STREPTOCOCCAL AGGLUTININS IN CHRONIC INFECTIOUS ARTHRITIS AND RHEUMATIC FEVER. E. E. NICHOLLS and W. J. STAINSBY, J. Clin. Investigation **10**:323 and 337, 1931.

The serums of patients with chronic infectious arthritis usually give a strong specific agglutination with "typical strains" of streptococci recoverable from the blood and joints of patients with this disease. Control serums do not show this reaction.

Chronic infectious arthritis can be differentiated from degenerative arthritis and from chronic polyarthritis following rheumatic fever by the agglutination reactions. These suggest different etiologies for the three forms of arthritis.

A close antigenic relationship between "typical strain" streptococci and the hemolytic streptococci from scarlet fever and erysipelas is established.

Additional evidence is presented in support of the theory that streptococci of the nonhemolytic type are important etiologic agents in rheumatic fever. This evidence consists in the demonstration of streptococcal agglutinins in the serums of patients with rheumatic fever.

Chronic progressive polyarthritis following rheumatic fever, although presenting a clinical picture similar to that of primary chronic infectious arthritis, gives evidence by agglutination reactions of being etiologically different.

Further evidence is presented of the etiologic relationship between the rheumatic fever and subacute bacterial endocarditis.

AUTHORS' SUMMARIES.

CULTIVATION OF VACCINE VIRUS FOR JENNERIAN PROPHYLAXIS IN MAN. T. M. RIVERS, J. Exper. Med. **54**: 453, 1931.

A dermal strain of vaccine virus has been adapted to a simple culture medium consisting of minced chick embryo suspended in Tyrode's solution. The bacteria-free culture virus thus obtained produces in lower animals and in man typical vaccinia that renders them refractory to infection with ordinary vaccine virus harvested from calves.

AUTHOR'S SUMMARY.

THE USE OF MICE IN TESTS OF IMMUNITY AGAINST YELLOW FEVER. W. A. SAWYER and W. LLOYD, J. Exper. Med. **54**: 533, 1931.

A method of testing serum for protective power against yellow fever is described and designated as the intraperitoneal protection test in mice. The test consists essentially of the inoculation of mice intraperitoneally with yellow fever virus, fixed for mice, together with the serum to be tested, and the simultaneous injection of starch solution into the brain to localize the virus. If the serum lacks protective power, the mice die of yellow fever encephalitis. The test is highly sensitive. Consequently it is useful in epidemiologic studies to determine whether persons have ever had yellow fever and in tests to find whether vaccinated persons or animals have been immunized. When mice were given large intraperitoneal injections of yellow fever virus fixed for mice, the virus could be recovered from the blood for four days, although encephalitis did not occur. If the brain was mildly injured at the time of the intraperitoneal injection, the symptoms of yellow fever encephalitis appeared six days later, but the virus was then absent from the blood. Strains of white mice vary greatly in their susceptibility to yellow fever.

AUTHORS' SUMMARY.

CUTANEOUS REACTIONS IN RABBITS TO THE TYPE-SPECIFIC CAPSULAR POLYSACCHARIDES OF PNEUMOCOCCUS. T. FRANCIS, JR., and W. S. TILLETT, J. Exper. Med. **54**: 587, 1931.

The injection of the type-specific capsular polysaccharides of types I, II and III of Pneumococcus into the skin of rabbits actively or passively immunized to one of these types of Pneumococcus elicits a type-specific cutaneous reaction. The form of reaction resembles that described by Arthus. The reaction is produced only when type-specific precipitins for the homologous polysaccharide are demonstrable in the blood of the rabbit. In 84 per cent of actively immunized rabbits the serum of which contained type-specific precipitins a reaction was elicited. A positive result was obtained in 100 per cent of rabbits passively immunized with antipneumococcus horse serum, whereas attempts to transfer reactivity from immune rabbit to normal rabbit passively were unsuccessful. In the latter group, the recipients possessed no demonstrable circulating type-specific precipitins. The reaction produced by specific capsular carbohydrates is always associated with well grounded type-specific immunity. A brief summary of the relation of hypersensitiveness and immunity to Pneumococcus is given.

AUTHORS' SUMMARY.

SERUM SICKNESS IN RABBITS. M. S. FLEISHER and L. JONES, J. Exper. Med. **54**: 597, 1931.

The injection of a single large dose of normal horse serum into rabbits results in the appearance from three to eight days later, of erythematous and edematous reactions on the ears in 68.9 per cent of the animals. The injections may be given by any of several routes, and reactions appear when the site of injection is definitely distant from the ears. Injections of various antiserums into rabbits cause the appearance of similar reactions. These reactions can be considered as manifestations of serum sickness in rabbits.

AUTHORS' SUMMARY.

ANTIBODIES IN THE SERUM OF RABBITS IMMUNIZED WITH HEAT-KILLED TYPE I PNEUMOCOCCI. E. G. STILLMAN, J. Exper. Med. **54**:615, 1931.

In rabbits immunized by the injection of suspensions of heat-killed pneumococci, the results obtained as regards not only the development of agglutinating and mouse protective antibodies, but also the persistence of these bodies in the blood, depend to a considerable extent on the route of immunization and the size of the inocula. Agglutinins may appear in the serums of all the rabbits except those inoculated subcutaneously, but in most instances they disappear within a short time. Protective antibodies appear in the serums of all rabbits, no matter which route of injection is employed, and they persist much longer than do the agglutinins. They persist longest when the injections are made intravenously or intraperitoneally and are of briefest duration when the injections are made subcutaneously.

AUTHOR'S SUMMARY.

LOCALIZATION OF PNEUMOCOCCI IN THE LUNGS OF PARTIALLY IMMUNIZED MICE FOLLOWING INHALATION OF PNEUMOCOCCI. E. G. STILLMAN and A. BRANCH, J. Exper. Med. **54**:623, 1931.

When mice are passively immunized by the intraperitoneal injection of antipneumococcus horse serum or actively by the injection of heat killed pneumococcus cultures, and are then alcoholized and sprayed with a culture of pneumococci of the same type as that of the bacteria employed in immunization, a considerable number die with localized lesions in the lungs. If instead of injecting immune serum of the type corresponding to that of the bacteria employed in producing the infection, normal horse serum or immune serum of a heterologous type is

injected, or if the animals are previously immunized by the injection of killed pneumococci of a heterologous type, none of the animals that died show any evidence of localization of the infection in the lungs. The occurrence of pulmonary lesions in alcoholized mice after they have been sprayed with a culture of pneumococci is the consequence of a general immunity of a very mild grade.

AUTHORS' SUMMARY.

CUTANEOUS REACTIONS AND CIRCULATING ANTIBODIES IN LOBAR PNEUMONIA. M. FINLAND and W. D. SUTLIFF, J. Exper. Med. **54**:637 and 653, 1931.

Patients with type I, II or III pneumococcus pneumonia who had not been treated with antiserum were studied with respect to their cutaneous reactions to specific pneumococcus polysaccharides, circulating agglutinins and protective antibodies for all three types. From one half to two thirds of the recovered patients gave the typical immediate response of wheal and erythema to the homologous type of pneumococcus. All patients tested showed protective antibodies, and almost all showed agglutinins, for the homologous organism. Patients whose pneumonia proved fatal failed to show the cutaneous reaction or circulating antibodies. In those receiving repeated cutaneous inoculations with various types of specific polysaccharide, antibodies differing from the infecting type were present, probably the result of immunization by cutaneous injections. Positive cutaneous reactions to homologous polysaccharides and similar circulating antibodies were found during the first three weeks after the crisis in patients who had not received intracutaneous injections. No heterologous antibodies were found in these patients. Typical cutaneous reactions and circulating antibodies were demonstrated in patients with no recent history of pneumonia. Patients with persistent or latent infections, later fatal, also gave positive reactions. The agglutination test, though less sensitive than the mouse protection test for determining the presence of antibody, is simplest to use in following the course of pneumonia in untreated patients. Cutaneous responses to type-specific, protein-free carbohydrates of types I and II pneumococci have been produced by the intravenous injection of concentrated bivalent antipneumococci serums. A positive cutaneous response to the specific polysaccharide of type II was passively transferred from convalescent patients to a patient with type II pneumonia. Positive cutaneous reactions were usually associated with recovery, and negative reactions with a fatal outcome. Positive reactions in patients treated with concentrated serums occurred twenty-four hours after the first dose. Positive reactions in patients receiving specific antiserums were associated with the presence of mouse protective antibodies and agglutinins in the serum. Of patients receiving repeated inoculations with the specific carbohydrates, serum-treated ones showed more rapid disappearance of immune reactions than patients receiving no antiserum. It is suggested that the antiserums administered interfere in some way with the production of antibodies following the intracutaneous injection of the carbohydrates.

EDNA DELVES.

LOCAL SKIN REACTIVITY: ANTIBODY AUXILIARY TO SERUM NEUTRALIZATION OF MENINGOCOCCUS REACTING FACTORS. G. SHWARTZMAN. J. Exper. Med. **54**:711, 1931.

In this paper there is described an antibody auxiliary to the neutralization of meningococcus factors. The presence of the antibody facilitates studies on the neutralizing potency of antimeningococcus serums. There is also reported a nonspecific neutralizing factor of a heterologous immune serum, which can be differentiated from specific neutralizing antibodies of antimeningococcus serums. Its nature and connection with auxiliary antibody remain to be determined.

AUTHOR'S SUMMARY.

A Serologic Study of the Polysaccharides of Meningococcus, B. Anthracis, B. Proteus, B. Subtilis and B. Mesentericus. J. Zozaya, J. Exper. Med. **54**:725, 1931.

The meningococcus polysaccharide reacts with a broad precipitable carbohydrate antibody in common with those of B. anthracis, B. subtilis, B. proteus and B. mesentericus. The anthrax and proteus polysaccharides are specific in the higher dilutions of serum. Antianthrax serum contains two different polysaccharide-precipitable antibodies, one specific and the other nonspecific. Agglutinins have no relation to the carbohydrate-precipitable substance, specific or nonspecific. An immunologic method is given for the study of the probable chemical relation or similarity of polysaccharides of different bacteria similar to that given by Heidelberger, Goebel and Avery for a strain of Friedländer's bacillus and Pneumococcus, type II.

Author's Summary.

Electrophoresis Experiments with the Virus and Protective Bodies of Yellow Fever. M. Frobisher, Jr., J. Exper. Med. **54**:733, 1931.

When suspended in slightly alkaline (p_H 7.4 to p_H 7.8) saline dilutions of clear, hemoglobin-free normal monkey serum, the virus of yellow fever from infected monkeys and from infected, but blood-free, mosquitoes usually acts as if it were possessed of a positive electrical charge. The virus tends to assume a negative charge in fluids having a slightly acid reaction. The iso-electric point of the virus seems to be in the neighborhood of p_H 7, possibly ranging from p_H 7.3 to p_H 6.9. Exposure to fluid having a reaction of p_H 5 for three hours appeared to inactivate the virus. In experiments in which the suspending fluid was prepared with normal serum diluted with distilled water and containing a considerable quantity of partly hemolyzed erythrocytes, the virus tended to migrate to the anode. The protective bodies in yellow fever immune serum appear to carry a negative charge in slightly alkaline saline dilutions of serum.

Author's Summary.

Granuloma-Like Allergic Inflammation. F. Roulet, Verhandl. d. deutsch. path. Gesellsch. **26**:189, 1931.

Fresh chicken blood was injected intraperitoneally at frequent intervals into guinea-pigs. From fifteen to twenty days after the last injection, the animals received intrapleural injections of from 2 to 3 cc. of antigen. Three different antigens were used; (1) whole chicken blood, (2) washed red corpuscles and (3) plasma. In the sensitized animals, the resorption of the antigen in the pleura was much slower than in the controls. Also the local reaction in the pleura appeared much later after sensitization. Histologically, the local reaction was found to consist of nodular granulomas with round cells, epithelioid cells and giant cells. These structures somewhat resembled tubercles, except that there was a much earlier production of connective tissue in the allergic granulomas.

C. A. Hellwig.

The Influence of Reticulo-Endothelial Blockade on Anaphylaxis. M. Haendel, Virchows Arch. f. path. Anat. **276**:22, 1930.

In guinea-pigs that had received intracardiac injections of india ink prior to a sensitizing injection of horse serum, the production of anaphylactic shock required an appreciably larger second dose of the serum than was required in control animals. A similar result was obtained if the sensitizing injection of horse serum preceded the treatment with india ink. The author concludes that the reticulo-endothelial system may play an important part in the formation of anaphylactic antibodies, and that an intact reticulo-endothelial system is necessary for the development of typical anaphylactic shock.

W. Saphir.

THE ACTION OF SERUM LIPOIDS IN THE ANAPHYLACTIC EXPERIMENT WITH THE GUINEA-PIG. R. OTTO and H. HOFFMANN, Ztschr. f. Immunitätsforsch. u. exper. Therap. **71**:233, 1931.

Otto and Hoffmann here furnish a check of the report of Mercier concerning the anti-anaphylactic and desensitizing action of serum lipoids. The protective effect was irregular. However, the value of the check is greatly reduced by considerable deviations from the original technic of Mercier. Serum lipoids alone failed to sensitize.

I. DAVIDSOHN.

CONGENITAL ANAPHYLAXIS IN THE GUINEA-PIG. R. DOERR and S. SEIDENBERG, Ztschr. f. Immunitätsforsch. u. exper. Therap. **71**:242, 1931.

Reports are confirmed that female guinea-pigs that have received subcutaneous injections of even very small doses of horse serum can give birth repeatedly to anaphylactic descendants during a period up to one and one-half years following sensitization. The young react to extremely small doses of the antigen and lose their reactivity between forty and seventy days after birth, presenting the characteristics of passive anaphylaxis. No explanation is offered for the long interval between sensitization of the mothers and the birth, though it is known that after the ninth week following injection no anaphylactic antibodies can be demonstrated in the mothers' blood. Active sensitization is rarely observed in the young and only when the mothers have been given an injection of a very large dose of the antigen shortly before delivery. In these occasional events, disturbances in the circulatory channels between mother and fetus may be responsible. Normal newborn guinea-pigs may be sensitized, though somewhat irregularly, with very small quantities of horse serum.

I. DAVIDSOHN.

SEROLOGIC STUDIES ON PUTREFACTION OF MEAT. FELIX SULMANN, Ztschr. f. Immunitätsforsch. u. exper. Therap. **71**:265, 1931.

The previously reported nonspecies-specific antigen of putrefaction could not be found in the products of peptic or tryptic digestion. The latter products were used as antigens in a complement-fixation test with an immune serum produced in rabbits treated with decayed meat. In a similar manner, the antigen was found in feces and possibly in urine. The antigen was not soluble in alcohol.

I. DAVIDSOHN.

SEROLOGY OF THE ISOAGGLUTININ SUBGROUPS A_1 AND A_2. V. FRIEDENREICH, Ztschr. f. Immunitätsforsch. u. exper. Therap. **71**:283, 1931.

The two subgroups within the group *A* found by Friedenreich and Worsaae (*Compt. rend. Soc. de biol.* **102**:884, 1929) are identical with A_1 and A_2 of Landsteiner, whose terminology is adopted. The A_2 is characterized by a lower agglutinability and constitutes about one fifth of the whole group A. The group AB is subdivided into A_1B and A_2B. The A_1 and A_2 are sharply separated from each other without transitions. The agglutinin anti-A has two fractions: α and α_1. Iso-agglutinins consist of numerous fractions, separable according to their avidity and thermal reactivity. The irregular agglutinin α_2 found occasionally in serums A_2 and A_2B behaves in its thermal reactivity like a "cold agglutinin" and in its specificity like a true iso-agglutinin. It seems to be identical with the lower fractions of the regular α_1 agglutinin.

I. DAVIDSOHN.

HOW IS THE OCCURRENCE OF ISO-AGGLUTININS REGULATED? V. FRIEDENREICH, Ztschr. f. Immunitätsforsch. u. exper. Therap. **71**:314, 1931.

An analysis of the various hypotheses leads to the conclusion that the "binding hypothesis" of Bernstein is best suited to explain the various phenomena: All

individuals produce both agglutinins α and β. The one that corresponds with the receptor in the same individual is being fixed by it and eliminated. This conception may be extended to all normal antibodies. The agglutinins are made up of a whole series of partial agglutinins reacting at various temperatures; the elimination of auto-agglutinins by fixation with homologous receptors is therefore limited by the range of body temperature, leaving the "cold-agglutinins" in circulation.

I. DAVIDSOHN.

THE HETEROPHILIC ANTIGENS IN PARATYPHOID BACILLI. KURT MEYER, Ztschr. f. Immunitätsforsch. u. exper. Therap. **71**:331, 1931.

The heterophilic hemolysins produced in rabbits by injections of various members of the paratyphoid group (groups: B, C and Gaertner) showed a strictly specific behavior, being fixed only by strains of the same group or even subgroup. The O (somatic)-antigens of the strains determined the character of the group or subgroup; the H-antigens were of no importance. The heterophilic antigen in the various bacteria (including B dysenteriae Shiga) does not react with the Forssman immune serums produced by injection of organs, while the guinea-pig organs and sheep red cells react with the bacterial immune serums. The explanation is offered that this is due to a combination of the Forssman antigen in bacteria with their specific carbohydrates, limiting their reactivity to immune serums produced by an antigen combined with the same carbohydrate. The hypothesis is to replace an older one of the existence of numerous partial antigens in the heterophilic antigen of the organs of the guinea-pig.

I. DAVIDSOHN.

THE IDENTITY OF THE HOUSE DUST ALLERGEN. A. PEIPERS, Ztschr. f. Immunitätsforsch. u. exper. Therap. **71**:359, 1931.

From a study of fourteen different house dust extracts it appeared that they contained many different allergens. Extracts of house dusts from regions with a large incidence of asthma were particularly efficient for skin tests. When house dust extracts were inhaled by asthmatic persons whose skin gave positive reactions, bronchial symptoms developed.

I. DAVIDSOHN.

EXPERIMENTAL LUETIN PARENCHYMATOUS KERATITIS. S. M. JENALEJEW, Ztschr. f. Immunitätsforsch. u. exper. Therap. **71**:365, 1931.

In rabbits and guinea-pigs treated with killed cultures of Spirochaeta pallida and in rabbits experimentally infected, injections of luetin into the cornea, about two weeks after the immunization was completed, produced a local inflammatory reaction. In guinea-pigs, the reaction was constant; in rabbits, somewhat irregular. After a short interval, a similar change appeared in the cornea of the other eye, which also was constant in guinea-pigs, but which occurred only in some of the rabbits.

I. DAVIDSOHN.

THE RETICULO-ENDOTHELIAL SYSTEM IN IMMUNITY IN RELAPSING FEVER. I. L. KRITSCHEWSKI and P. L. RUBINSTEIN, Ztschr. f. Immunitätsforsch. u. exper. Therap. **71**:372, 1931.

Splenectomy alone and in combination with blockade of the reticulo-endothelial system did not decrease the immunity in mice that had become resistant as a result of a previous infection. Animals not previously infected or those that developed no immunity despite infection succumbed to the disease when the spirochetes were injected after splenectomy or blockade, or a combination of the two.

I. DAVIDSOHN.

Tumors

ULTRAFILTRATION OF THE AGENT OF CHICKEN TUMOR NO. 1. WILLIAM MENDELSOHN, C. E. CLIFTON and M. R. LEWIS, Am. J. Hyg. **14**:421, 1931.

The active principle of chicken tumor no. 1 readily passed through 0.5, 1, 2 and 3 per cent collodion membranes. In one instance it passed the 5 per cent collodion membrane. The filtrates that passed through the 4 and 5 per cent collodion membranes were free from demonstrable protein. The size of the particles of the agent of chicken tumor no. 1 was found to be less than 50 millimicrons and possibly less than 15 millimicrons.

AUTHORS' SUMMARY.

IMMUNITY TO WALKER'S RAT SARCOMA NO. 1. F. DONAGHY and R. R. HYDE, Am. J. Hyg. **14**:495, 1931.

Study of three races of rats revealed that the one (Philadelphia) is susceptible to Walker's rat sarcoma no. 1, whereas two other races of rats are immune in a high percentage of cases. Attempts to immunize the susceptible Philadelphia rats were made (1) by removing the implant after it had grown in the host for some time; (2) by feeding tumor tissue; (3) by feeding tissues from resistant rats; (4) by the injection of immune serum from the rabbit and the guinea-pig; (5) by injection of serum and whole blood from chickens treated with sarcoma no. 1; (6) by treatment with embryo skin; (7) by treatment with an emulsion of spleen from tumor-bearing animals; (8) by passage of tumor fragments through the resistant host, and (9) by nursing the young of the susceptible Philadelphia stock on tumor-bearing mothers. In all cases the animals remained susceptible to Walker's rat sarcoma no. 1.

PAUL MERRELL.

IMPLANTATION PERITONEAL CARCINOMATOSIS OF OVARIAN ORIGIN. J. A. SAMPSON, Am. J. Path. **7**:423, 1931.

Implantation peritoneal carcinomatosis arises from the repair of injuries to the peritoneum caused by cancer cells which have escaped into the peritoneal cavity and lodged on the surface of its serous membrane, together with the continued growth of these cells in this situation. The various stages in this repair, as well as the laws governing the same, are similar to those encountered in the repair of tissues injured by foreign bodies, and in the taking of skin grafts, namely, the healing of wounds. The histologic structure of these implants varies with the reaction of the peritoneal tissues before and after the fixation of the cancer cells and the activity of the latter. As a result, cancer becomes embedded in the peritoneal scar, encapsulated on its surface and enmeshed in adhesions, or, like the epithelial growth of a successful skin graft, spreads over the peritoneum without encapsulation. The malignant cells of these metastatic tumors possess the same potentialities of invasion and dissemination as those of a primary cancer.

AUTHOR'S SUMMARY.

THE NATURE OF HODGKIN'S DISEASE. E. M. MEDLAR, Am. J. Path. **7**:499, 1931.

Evidence is presented which suggests that Hodgkin's disease is a malignancy of the bone marrow. The type cell appears to be the megakaryocyte. The developmental cycle of the megakaryocyte is presented. It would seem that the typical megakaryocyte is the result of fusion of several premegakaryocytes. The histopathology of Hodgkin's disease is a pleomorphic aggregation of cells which represent the developmental cycle of the megakaryocyte. It is not essential to have fibrosis or eosinophilic or neutrophilic infiltration to establish the diagnosis of Hodgkin's disease. The involvement of lymph nodes and other tissue outside

of the bone marrow appears to be metastatic tumor growth. Evidence is presented which tends to prove that all blood cells arising from the marrow have a common parent cell. The term "megakaryoblastoma" is suggested to designate true Hodgkin's disease.

AUTHOR'S SUMMARY.

THE EFFECT OF TESTICLE EXTRACT ON THE ROUS SARCOMA. D. C. HOFFMAN, FREDERIC PARKER, JR., and T. T. WALKER, Am. J. Path. **7**:523, 1931.

Rabbit testicle extract markedly enhances growth of the Rous sarcoma (chicken tumor I) in chickens. This effect is the same whether tumor mash or a cell-free filtrate of the tumor is used in the inoculations. Rooster testicle extract causes no enhancement. Normal rabbit serum causes a slight degree of enhancement.

AUTHORS' SUMMARY.

TUMORS OF THE EXTRAHEPATIC BILE DUCTS. P. F. SHAPIRO and R. A. LIFVENDAHL, Ann. Surg. **94**:61, 1931.

Fifteen tumors of the extrahepatic bile ducts were encountered in 2,500 necropsies. Of these one was an amputation neuroma, one a solid adenoma, one a congenital cyst of the cystic duct and twelve carcinomas. According to this material, carcinoma of the extrahepatic bile ducts was twice as common as carcinoma of the gallbladder and three times as common as cancer of the head of the pancreas and comprises 3.7 per cent of all cancers. In the cancers the clinical course for those in the extrahepatic bile ducts averaged 5.3 months; 60 per cent occurred in males, and 71 per cent in white persons, at an average age of 59.7 years. The percentage figures for males, etc., are corrected sex and race differences. Twice as many necropsies were held on males as on females, and twice as many on white people as on colored. Contrary to the usual opinion, metastases occurred frequently and early and often were extensive so as to dominate the clinical picture. No difference was noticed between scirrhous or polypoid tumors in their tendency to intramural growth, their histologic structure or their tendency to metastasize.

GEORGE RUKSTINAT.

THE GANGLIONEUROMAS OF THE CENTRAL NERVOUS SYSTEM. BERNARD J. ALPERS and FRANCIS C. GRANT, Arch. Neurol. & Psychiat. **26**:501, 1931.

Alpers and Grant describe a case of ganglioneuroma, a tumor classified by Virchow as true neuroma but lately as ganglioglioma and ganglioglioneuroma. The patient was a boy, aged 16, who had suffered from paroxysmal frontal headaches and later from attacks of blindness of one or two minutes' duration. The boy finally became blind. He had frozen pupils and signs of a brain tumor, which was localized in the pituitary region with endocrine disturbances, soft, smooth skin, hips of the feminine type, a feminine distribution of the pubic hair, only little axillary hair and rather prominent breasts. The tumor was partially removed. It contained numerous ganglion cells, some of which were apolar, some bipolar or multipolar. There were many small cells, evidently glia, numerous blood vessels and nerve fibers, mostly nonmedullated. The cells in ganglioneuromas are regarded not as neuroblasts but as immature ganglion cells which for some reasons failed to develop.

GEORGE B. HASSIN.

BASOPHILIC ADENOMA OF THE HYPOPHYSIS WITH ASSOCIATED PLURIGLANDULAR SYNDROME. HAROLD M. TEEL, Arch. Neurol. & Psychiat. **26**:593, 1931.

The anterior lobe of the hypophysis is known not only to possess gonad-stimulating properties but also to have some influence on other endocrine organs, such as the suprarenal cortex and thyroid. The substance responsible for the

gonad-stimulating effect is elaborated in basophilic cells of the anterior lobe. As the case reported by Teel shows, a basophilic adenoma of the hypophysis may be associated with hypertrophic changes in the endocrine organs. A white woman, aged 20, had convulsions and became unconscious, after two days of chills, fever and vomiting. The weight was increased (206 pounds), the basal metabolism was plus 42, and there was excessive growth of hair on the face, thorax, abdomen and extremities. The patient died of cerebrospinal meningitis. The hypophysis showed at its lateral inferior margin a nodular collection of basophilic cells measuring 2.5 mm. in diameter. The surrounding glandular tissue was compressed and atrophied. The thyroid, thymus and suprarenals were enlarged, the pancreas showed an unusually large number of islets, and the ovaries, which were much larger than usual, contained numerous small follicular cysts.

GEORGE B. HASSIN.

GLIOMAS OF THE RETINA. ROY R. GRINKER, Arch. Ophth. **5**:920, 1931.

Heretofore, cellular studies of retinal gliomas have failed to reveal the exact type of glia cells within tumors because sections embedded in celloidin and stained with hematoxylin-eosin have been almost exclusively used. Fixation in formaldehyde and silver impregnations of frozen sections are essential to demonstrate the cell processes and their relations to blood vessels and each other. With these methods gliomas of the retina possibly can be classified according to the normal histogenetic stage of the retina. Such a classification may be utilized in correlation with the clinical and biologic characteristics of the component cells to great advantage.

The glial tumors of the retina now known are divisible into three large groups. The medullo-epitheliomas consist mostly of primitive retinal epithelium, which persists in adult life as ciliary epithelium and from which thesetumors arise, and also of neuro-epithelium and retinoblasts. Retinoblastomas are chiefly composed of retinoblasts. In the tumors composed of these indifferent cells, evolutionary stages in the histogenesis of adult retinal glia have been found, but no cells of the ganglion series have as yet been described. In the neuro-epitheliomas, spongioblasts are found in rosette-like arrangement. These cells closely resemble the rods and cones. Primitive spongioblasts, astroblasts, astrocytes and oligodendroglia are also found, all normally derived from the neuro-epithelium. A histogenesis of glia possibly occurs in these tumors, but each group contains a preponderance of the more primitive types of cells. Tumors of pigmented epithelium have not been described, possibly because the epithelial cells lose their pigment in neoplasms. Other types of tumors probably will be revealed with further study of more material.

AUTHOR'S ABSTRACT.

THE EFFECT OF TISSUE EXTRACTS ON THE RESPIRATION OF TUMOR TISSUES. L. J. SOFFER, Bull. Johns Hopkins Hosp. **49**:320, 1931.

The accelerating effect of rat liver extract and to a lesser extent of kidney extract on the oxygen consumption of mature erythrocytes has been confirmed. Methylene blue (methylthionine chloride, U. S. P.) increases the oxygen consumption of tumors (of carcinomas more than of sarcomas), while it exercises no such effect on normal tissues. Liver extract, homologous and heterologous, fails to increase the respiration of either tumors or normal tissues.

AUTHOR'S SUMMARY.

THE MELANOMAS OF GREY AND WHITE HORSES. S. HADWEN, Canad. M. A. J. **25**:519, 1931.

The pigmentary systems of horses and man differ. Animals are entirely clothed with hair and shed it annually. Horses that whiten with age are predisposed to melanomas. The tumors progressively increase in size with age. This is associated with continued melanin production, though the hair no longer makes

use of it. The melanomas begin to form when horses are still young, 6 years or over. The deposits are found in avascular places. They are common in the perineum. Other abnormalities in color occur on the line of union between the two halves of the body. White marks are strongly inherited. The commonest sites for melanomas are in the regions of the tail and mane. It is improbable that this is due to irritation from the harness, as has been suggested, but more likely that a larger flow of tyrosine is being directed to these parts. Freckles in horses depend on exposure to sunlight, length and color of hair and to age. As they ascend to the corneum, the columnar basal cells of the epidermis lose their strands of melanin and alter their shape. At the edge of leukodermic areas the basal cells produce melanin irregularly; some overproduce; others are unable to form pigment. Melanic masses may form extensions through pressure from outside the body. The sweat glands may be destroyed by melanin, but the subaceous glands are not infiltrated. In deep situations the melanoblasts are spindle-shaped, having long processes and coarser melanin than one finds in the epidermis. Many types of cells, such as the basal cells, are round when no pressure is exerted on them. It is believed that many varieties of so-called atypical cells are in reality normal cells that have been molded out of shape through pressure or the release of pressure exerted by edematous fluids or overgrowth. Through overproduction of melanin, the basal cells of the epidermis may become disarranged and appear atypical. Melanomas in horses rarely become malignant.

AUTHOR'S SUMMARY.

THE BLOOD OF NORMAL RABBITS AS AN INDEX OF THEIR RESISTANCE TO A TRANSPLANTABLE NEOPLASM. A. E. CASEY and L. PEARCE, J. Exper. Med. **54**:475, 1931.

The blood cytology of ninety-one rabbits was studied prior to inoculation with a transplantable malignant neoplasm. The following statements refer in each instance to the mean values of the preinoculation counts. The animals that were most resistant to the malignant disease had, before inoculation, normal red and white cell counts, normal hemoglobin percentages, high eosinophil counts and low counts of monocytes and lymphocytes. The relations of the neutrophil and basophil counts were irregular, but normal values also appeared to be associated with greater resistance. The most susceptible animals were those that had, before inoculation, red cell counts above 5,500,000 or below 5,000,000 per c.mm.; hemoglobin above 70 per cent or below 60 per cent (Newcomer); white cell counts below 6,000 or above 8,500 per c.mm.; low eosinophil, high monocyte or high lymphocyte counts. No animal with any of the following findings prior to inoculation recovered completely from the tumor as determined by autopsy examination, red cells above 5,500,000 per c.mm. of blood; hemoglobin above 70 per cent; total white cells above 10,000 per c.mm.; eosinophils below 120 per c.mm., or below the relative value of 1.5 per cent; basophils below 400 per c.mm., or below the relative value of 6 per cent; lymphocytes above 3,600 per c.mm.; monocytes above 1,500 per c.mm.; neutrophils above 5,000 per c.mm., and total granular cells above 5,700 per c.mm. In the case of each the following preinoculation values, only one animal was completely free from tumor at autopsy: hemoglobin below 60 per cent, red cells below 4,800,000 per c.mm., total granular cells below 3,300 per c.mm., total nongranular cells below 2,300 per c.mm. and total nongranular cells above 3,700 per c.mm. No animal with preinoculation eosinophils above 3.9 per cent or basophils above 16 per cent died from the tumor. The blood findings before inoculation could be related to the character and outcome of the malignant disease, from the standpoint of animal groups as well as in the case of individual rabbits. From the results of the experiments here reported, it seems possible to predict with an accuracy of between 80 and 90 per cent the individual resistance or susceptibility of rabbits to the tumor by a study of their blood cells before inoculation.

AUTHORS' SUMMARY.

EPITHELIOMA AND SARCOMA OF THE STOMACH. A. KLEINKNECHT, C. OBERLING and S. TASSOWATZ, Bull. Assoc. franç. p. l'étude du cancer **20**:209, 1931.

If one is to judge from the cases reported in the literature, multiple tumors of this kind have a predilection for certain organs such as the uterus, the breast, the esophagus and the thyroid gland.

In the case reported, it concerned a linitis plastica and a leiomyosarcoma. The topographic relationship of the two tumors was very intimate, and the authors believe that the gastric cancer has led to the sarcomatous transformations of the mesenchymal element of the stomach with which it came in contact.

B. M. FRIED.

ANGIOMA OF PIA OF CEREBELLUM. A. DE BLASI, Pathologica **23**:18, 1931.

A case of a tumor in the pia mater of the cerebellum in a man, aged 74, is reported. The histologic picture was that of capillary angioma with numerous nests of small round cells between the capillaries. The origin of the cell nests could not be determined.

E. HAAM.

PRODUCTION OF TUMORS IN URINARY BLADDER IN RATS. E. PUCCINELLI, Pathologica **23**:73, 1931.

In twenty-six rats, a bolus consisting of tar, paraffin and scarlet red was introduced into the urinary bladder. The animals were subsequently given subcutaneous injections of solutions of arsenous acid and tar. In three cases, papillomatous growths showing keratinization were observed, but in no case did a malignant tumor develop.

E. HAAM.

PAPILLARY CYSTADENOMA OF THE PANCREAS. F. TAVERNARI, Pathologica **23**:207, 1931.

The author reports a case of papillary cystadenoma, without signs of malignancy of the pancreas, in a woman, 72 years old. The genesis of the tumor was probably due to a congenital abnormality of the cells of the excretory ducts.

E. HAAM.

ARE BIOPSIES ON MALIGNANT TUMORS DANGEROUS? A. EPSTEIN and A. FEDOREJEFF, Arch. f. klin. Chir. **165**:357, 1931.

Between October, 1926, and June, 1930, 1,581 biopsies were made at the Oncologic Institut in Leningrad. In 1,222 cases this was done once, and in 359 patients repeatedly. The clinical diagnosis of malignancy was substantiated by the pathologist in 81.7 per cent.

Fever after biopsy was observed in 4 per cent of 1,226 cases of carcinoma and in 19 per cent of 53 cases of sarcoma. In two cases biopsy was followed by severe infection. Fatal infection occurred in one case of carcinoma of the uterus with extensive metastases. In three carcinomas and in one sarcoma the diagnostic incision seemed to accelerate growth; however, all these four cases were late forms with ulceration and in the two carcinomas of the breast there was also widespread metastases before biopsy. Very slight hemorrhages, easily controlled by gauze, occurred nineteen times; no severe hemorrhage was observed in the whole series of biopsies. To avoid any possible danger, the authors recommend the electric knife for diagnostic incisions, and they cauterize the wound with concentrated phenol. The immediate diagnosis from frozen sections during operation is regarded as the method of choice. In accessible tumors, the enlarged regionary lymph glands are excised for diagnosis. In oral and laryngeal cancer, radiation treatment is initiated before biopsy.

The authors conclude from their observations and from a review of the literature that complications after well performed biopsy are exceptional. There is some danger of acceleration in growth following biopsy, especially in sarcoma. If ever possible, radical operation should follow immediately the diagnostic incision. In tumors of the breast, biopsy should not be performed as an independent operation, but the histologic diagnosis should be made during operation from frozen sections. Radiation treatment, if indicated, should precede the diagnostic incision. In tumors covered with intact skin, enlarged regionary lymph glands may be excised without danger for diagnostic purposes.

C. A. HELLWIG.

Medicolegal Pathology

THE RELATION OF PATHOLOGY TO LEGAL MEDICINE. Z. E. BOLIN, California & West. Med. **35**:195, 1931.

Bolin contrasts the unsatisfactory state of legal medicine in this country with the organization and importance of medicolegal science in Europe as a university discipline and as a function of the state. He suggests a plan of correlated organization of the essential elements of existing university activities into a provisional university department of legal medicine. Such a department should, at least at first, be a subdivision of the department of pathology, because of the dominant share of this science in medicolegal work. It should be under the direction of a pathologist, whose duty it would be to correlate the necessary activities of other medical and university departments into an organization capable of providing adequate instruction in the subject. One or more graduates in law could present the legal aspects. The facilities of the department would be offered to the police and coroner, whose material should be made available to the department for teaching purposes. The teaching could be condensed within a single year or spread over the four years of the medical course. The organization proposed would entail no great expense on the university, because it would make use of personnel and facilities that the university has. By the time that the duties of the department of legal medicine had become more onerous, it would have established its claim to more liberal financial support by service rendered in teaching and in the administration of justice.

O. T. SCHULTZ.

UNEXPECTED AUTOPSY RESULTS IN UNEXPECTED DEATHS. W. J. DEADMAN, Canad. M. A. J. **25**:317, 1931.

From a series of about 1,200 autopsies over a period of ten years, the following cases are presented in view of the unexpectedness of the deaths and the unusual autopsy results, together with as much of the clinical history and findings as possible: extreme fatty degeneration of the myocardium in a 17 year old girl, following arsenical therapy in syphilis; traumatic hematopericardium following a traumatic, nonbleeding puncture wound of the chest; aortic stenosis in a 45 year old man with no history of previous illness; congenital absence of the ventricular septum in a 3 day old infant; coronary thrombosis in a 14 year old girl following violent exercise, the origin of the thrombosis being vegetative masses at the mouth of the left coronary artery; lobar pneumonia in a workman who collapsed on duty; influenzal pneumonia, hemorrhagic, in a middle-aged man who collapsed at work; glioma of the cerebellum in a patient who died during a diagnostic spinal puncture; hemorrhage into a cerebral cyst following a slight contusion of the head in a young man of 24; death by suffocation in epilepsy following an attack in a man in whom epilepsy had never been suspected; appendical hemorrhage in which a "common pin," evidently swallowed, had eroded through a small vessel and the appendical wall, causing hemorrhagic peritonitis; infected Meckel diverticulum as the point of incitement of "idiopathic" peritonitis; traumatic rupture of the spleen following a fall from a horse, in a young soldier who had had previous attacks of malaria; "status thymicolymphaticus" in a 12 year old boy

who had apparently been drowned following a blow from a row-boat oar which caused him to fall overboard; rupture of the posterior wall of the duodenum in a person who was crushed against the wall of a sand-pit by the hub of a wagon wheel.

WILLIAM FREEMAN.

SUDDEN DEATH IN ASYMPTOMATIC SUBACUTE BACTERIAL ENDOCARDITIS. G. L. WEST, New England J. Med. **205**:675, 1931.

A woman, 31 years of age, an expert swimmer and athletic instructor, while playing tennis, became suddenly weak, cyanotic, then unconscious and died within an hour. Post mortem, many friable endocardial vegetations were found. At the bifurcation of the left coronary artery, there was an embolus from a vegetation, triangular in shape and 10 by 5 by 5 mm., occluding both branches of the artery distal to the bifurcation. Cultures from the vegetative growths and the embolus gave gram-positive cocci, occurring singly and in chains.

WILLIAM FREEMAN.

A CASE OF POISONING BY SODIUM NITROPRUSSIDE. F. S. FOXWEATHER, Brit. M. J. **2**:344 (Aug. 22) 1931.

This is the first recorded death by poisoning with sodium nitroprusside. The patient soon became unconscious; respirations were slow and irregular, with heavy and short inspirations and prolonged expirations. The pupils reacted sluggishly and were moderately dilated. There were subnormal temperature and slow pulse. Death occurred in two and one-half hours after ingestion of the poison. There were no convulsions. Postmortem examination elicited a marked odor of hydrogen cyanide gas on opening the body. The gastric contents gave off a hydrogen cyanide odor. The condition of the tissues was consistent with hydrogen cyanide poisoning.

WILLIAM FREEMAN.

AUTOPSIES OF UNUSUAL INTEREST. I. B. MORRIS, Lancet **2**:737, 1931.

The author presents several instances of unusual conditions found at autopsy in cases of sudden death, namely, spontaneous rupture of the aorta in a man aged 49; primary carcinoma of the bronchus with extensive invasion of the lung and mediastinum with rupture into the pericardium in a man aged 42; impacted gallstone in the ampulla in a 65 year old woman; acute extensive miliary tuberculosis in a man aged 61.

WILLIAM FREEMAN.

SUDDEN DEATH FROM INTERSTITIAL CARDIAC HEMORRHAGE. F. MOOR, Lancet **2**:740, 1931.

In a woman, aged 68, who eight months prior to death had pain in the chest, apparently due to bruising of the right wall of the chest, the only other sign found was a moderately hypertrophied heart and hypertension. During the succeeding interval, the patient enjoyed fair health and died suddenly. The heart revealed calcareous deposits and stenosis of the proximal ends of each coronary vessel so that a probe tip could be passed, but no thrombosis. The lower right portion of the interauricular septum showed rather extensive areas of hemorrhage beneath the endocardium and elevating it for a short distance. The hemorrhage appeared to be of too recent origin to be related to the previous accident.

WILLIAM FREEMAN.

INHERITANCE OF PAPILLARY PATTERNS OF THE PALM AND FINGERS. B. MUELLER, Deutsche Ztschr. f. d. ges. gerichtl. Med. **17**:407, 1931.

In cases of questionable paternity, in addition to the blood grouping tests, the analysis of the papillary lines of the fingers and of the palmar ridges may, under

certain favorable conditions, be used to advantage. The Gruenberg theory in regard to the inheritance of papillary arch formations is critically discussed and evaluated. The important work of Poll and his classification of various patterns are emphasized, since he seems to prove that, in particular instances, by a comparison test of papillary patterns of persons involved (mother, child and questionable father), the accused man may be excluded as parent of the child.

E. L. MILOSLAVICH.

URIC ACID INFARCTS IN THE STILLBORN INFANT. M. BOGEN, Deutsche Ztschr. f. d. ges. gerichtl. Med. **17**:426, 1931.

Ever since the first observations of Virchow (1847), it has been thought that uric acid infarcts are found only in new-born infants who have breathed, and consequently a certain medicolegal significance has been attached to such infarcts. But as far back as 1900, the Hektoen and Riesman textbook emphasized that such infarcts occur also in stillborn infants. The appearance of uric acid infarcts in kidneys of infants who die shortly after delivery seems to have a certain relation to uric acid formation due to disintegration of large numbers of leukocytes, since in the first days of extra-uterine life there is pronounced leukocytosis. The author describes a pertinent case of a full term but stillborn child, whose dead body was delivered by means of cephalotripsy. Because of the protracted delivery in this case, it is assumed that, as demonstrated in such instances by Schwarz and Mausloff, the umbilical blood contained a large amount of uric acid, which, in connection with disintegration of large numbers of leukocytes, might cause the infarcts, regardless of whether the child was born alive or dead.

E. L. MILOSLAVICH.

Technical

PRESERVATION OF HEARTS BY PARAFFIN INFILTRATION. L. GROSS and E. LESLIE, Am. Heart J. **6**:665, 1931.

The interior of the unopened heart is first examined with a nasoscope, and postmortem blood clots are removed. Fixation is accomplished by perfusion of the organ with neutral formaldehyde solution for seventy-two hours through a system of cannulas by which, also, the heart is suspended in the formaldehyde solution and filled with it until the walls take their natural shape. After dehydration for from two to four days in increasing percentages of alcohol, the heart is put through two changes of toluene in seventy-two hours; it is then placed in a bath of 5 parts of beeswax and 95 parts of paraffin at 56 C., renewed once in forty-eight hours. While the heart is still warm, incisions are made, allowing exposure of the interiors of the chambers by removal of their outer walls. The coronary arteries are opened during the dehydration in alcohol. Blocks for microscopic study are removed after fixation in formaldehyde or, preferably, after paraffin infiltration, while the tissues are still warm.

E. M. BARTON.

PREVENTING DEHYDRATION OF CULTURE MEDIUMS. W. KRANTZ, Dermat. Wchnschr. **93**:1263, 1931.

The medium is placed on the bottom of a small Erlenmeyer flask fitted with a cord tightly sealed in with paraffin. A narrow glass tube of inverted U shape is fitted into the single hole in the cork and also sealed in with paraffin. Cultures have been kept for five years without dehydration of the medium. A tiny drop of water of condensation collects on the tip of the tube in the flask.

LAWRENCE PARSONS.

Society Transactions

NEW YORK PATHOLOGICAL SOCIETY

Regular Meeting, Nov. 14, 1931

LEILA CHARLTON KNOX, President, in the Chair

A CASE OF GENERALIZED NECROSING ARTERITIS. CHARLES T. OLCOTT.

A 12 year old white girl of English extraction had symptoms pointing to pyelitis eleven months before admission and pharyngitis one month before admission. Her heart seemed enlarged. The temperature rose almost daily to 103 F. The red blood cells were 3,000,000, with 40 per cent hemoglobin; the white cells were 20,000, with 84 per cent polymorphonuclear leukocytes. The urine showed albumin in large amounts and many pus cells. The blood urea nitrogen rose from 50 to 106 mg. per hundred cubic centimeters. Blood cultures were negative, but one urine culture showed nonhemolytic streptococci. The patient vomited persistently; the urinary output decreased; convulsive attacks developed, and she died three weeks after admission. The Wassermann reaction was negative. The clinical diagnosis was nephritis.

At autopsy there were edema of the lungs and ascites. Reddish zones, about 2.5 cm. in diameter, were found on the surface of the liver, and in these there were elevated white masses of pinhead size. The kidneys were mottled, partly dark red and partly light red. The darker red areas contained elevated white masses similar to those in the liver. These were found on the surfaces and in the deeper portions of the kidneys. No gross findings demonstrated the nature of the process.

Histologic study (illustrated by lantern slides), however, demonstrated marked changes in the arteries of the liver, kidney, appendix, heart and pleura and in a branch of the abdominal aorta. These showed hyalinization and thickening of the medial coats with, in some cases, destruction of both elastic laminae. Marked infiltration of the adventitial layers by polymorphonuclear cells, lymphocytes and eosinophils was present. Intimal changes varied in degree. In some cases, notably in the kidney, intimal proliferation markedly diminished the lumina of the vessels, while in others the intima was normal. No thrombosis or aneurysmal dilatation was found. Associated with the vascular lesions of the kidney and liver were hemorrhagic infarcts. The cytoplasm of some of the liver cells and some of the muscle fibrils of the heart showed bluish staining in hematoxylin and eosin preparations.

A postmortem blood culture was positive for an hemolytic streptococcus, but this was considered as probably a late invader. Bacterial stains of the tissues failed to demonstrate any specific etiology. This is in accordance with the observations of the majority of observers. A hypersensitization phenomenon cannot be excluded.

Summary.—A case of necrosing arteritis of renal, hepatic and other vessels is presented. Presumably because of the patient's rapid death, there was no development of the nodular aneurysmal dilatations characteristic of periarteritis nodosa. In other respects the case belongs in that group.

DISCUSSION

MORGAN VANCE: I was much interested in Dr. Olcott's case as an example of periarteritis nodosa without the nodosities. The majority of cases are a mixture of necrotic arteritis and aneurysm formation in some of the small vessels in different parts of the body, namely, in the heart, liver, kidneys, mesentery, intestines

and elsewhere. The disease is a rather complicated one, and I do not wish to take time to discuss it in detail, but I have three lantern slides of a case Dr. Graham and I reported recently in THE ARCHIVES (**12**:521, 1931). This case is one of the more orthodox types of periarteritis nodosa, in that it shows multiple aneurysms and also the formation of multiple infarcts in the liver and kidneys.

PAUL KLEMPERER: We have made some observations on this subject in the last years at the Mount Sinai Hospital, and Dr. S. Otani has collected most of our cases for the exhibit at the recent Graduate Fortnight of the New York Academy of Medicine. We have had eleven cases in the last five years; nine of them and an earlier case that Dr. Otani included were shown. The most interesting fact is that the number of cases has increased so remarkably in the last ten years. Up to then individual cases were reported because the condition was considered unusual enough to justify the report of a single case. In the last few years, the number of reports has gone up markedly. I think this is due to the fact that we reserve the diagnosis periarteritis nodosa not only for cases in which the arterial lesion is classic, according to the original description by Kussmaul and Mayer, but also—and correctly—for cases of generalized necrosing arteritis without aneurysm formation. I think one should abstain from referring to this type of vascular disease as periarteritis nodosa, because the actual gross lesion is not so frequently found and is not always so conspicuous as it is said to be in the original description. In the group of cases that Dr. Otani showed there were only three cases in which aneurysms were seen so that the diagnosis of periarteritis nodosa in the classic sense was justified. In one of these, aneurysms about the size of a cherry and even larger were shown in the kidney. In other cases, arterial lesions could be seen with the naked eye only with difficulty. However, one could easily recognize them if one used a magnifying glass on the gross specimen. The use of a magnifying lens was indicated because of multiple infarcts in the kidneys and other organs that were apparently not of embolic origin. In all these cases, the appearance of the infarct-like lesions suggested a search for a primary vascular change. In nearly every one of these instances, arterial lesions could then be demonstrated in the gross. Macroscopically, they did not impress one as aneurysms so much as focal thickenings of the arteries. The interlobar arteries of the kidneys showed lesions frequently. We nearly always found them in the mesenteric arteries just at the insertion of the branch of the mesenteric artery into the intestine. One place in which we looked for them was the gallbladder, in which they were present frequently. I think that by routine histologic examination one would find much more necrosing arteritis than would be suggested by the gross appearance. Aneurysms are not so frequent, but the necrosing arteritis demonstrated on minute examination of the gross material, or only histologically, is not so rare.

Most interesting, it seems to me, is the relationship that exists between renal symptoms and necrosing arteritis. In Dr. Olcott's case, the renal symptoms were the leading ones; there was apparently no nephritis. However, it is peculiar how frequently diffuse glomerulonephritis is combined with generalized necrosing arteritis. In three of our cases there were diffuse glomerulonephritis of typical appearance and generalization of the arterial disease. This is particularly interesting because glomerulonephritis shows not infrequently (in about from 10 to 20 per cent of cases) in the subacute stage a lesion in the smaller arteries, the afferent vessels, that is identical with the necrosing lesion of the generalized type described. This might throw some light on the pathogenesis of the disease; that is, that it is of the same pathogenesis as glomerulonephritis, namely, toxic. I realize that one usually has not paid particular attention in this disease to the history of the patient in regard to the question of antecedent infection, which if found would suggest that a peculiar stage of sensitization has been caused by the previous infection, which at the recurrence of infection, perhaps identical or of different etiology, leads to this peculiar necrosis of the blood vessels. It might be worth while to mention in this respect two cases of rheumatic fever with Aschoff bodies in the myocardium and verrucous endocarditis in which systemic

necrosing arteritis was found. In both cases there were certain clinical peculiarities that caused the clinicians to doubt the diagnosis of rheumatism, though there was otherwise considerable evidence in favor of it. In both cases, during the progress of the disease, pain was particularly conspicuous in various parts of the body, which is not, as far as I am informed, considered typical of rheumatic heart disease. In both instances there existed a generalized arterial disease of the same type as that described tonight. In one case, it was found only on close study of the histologic sections; in the other case, in which the disease of the arteries was particularly conspicuous in the lungs, the lungs were riddled with small nodules, arranged around the blood vessels. I think such findings of necrosing arteritis in rheumatism are particularly interesting because of the reports of von Glahn and Pappenheimer on arteritic lesions in rheumatism. I have always thought that they were not specific for rheumatism but had something to do with the peculiar evolution of rheumatism, especially with the recurrent type of disease that rheumatism is.

I feel that we should not look for a specific bacteriologic etiology in necrosing arteritis, but should search for a specific immunologic phase or a specific sensitiveness of the blood vessels, and try to reproduce this, if possible, experimentally, instead of trying to reproduce the disease by the injection of organ extracts in such cases.

Two other cases suggest a similar pathogenic principle. In both instances, there had existed a severe sinusitis for a long time, and the terminal disease, proved at autopsy to be general necrosing arteritis, had begun shortly after some operation on the nasal sinuses. It was possibly due to this operation that a new invasion of toxins into the blood stream had been caused.

In regard to the clinical diagnosis in our eleven cases, the diagnosis was made during life only once. This was in a case in which there were numerous large aneurysms of the kidneys, causing severe hematuria. In this instance, Dr. Edwin Beer suggested the diagnosis of periarteritis nodosa. In the other cases, the diagnosis was made only at the autopsy table.

ALFRED PLAUT: Dr. Klemperer's remarks strongly emphasize the nonspecific nature of periarteritis nodosa. Several years ago, I was struck by peculiar lesions of the arterioles in the vermiform appendix that resembled periarteritis nodosa. These lesions were demonstrated at a meeting of the American Association of Pathologists at Albany. Meanwhile the same lesions have been found in many routine specimens of the appendix vermiformis and occasionally in specimens of the internal female genital organs. They may be designated as focal, nonspecific arteriolitis. I have never seen them in veins or in any medium-sized or large arteries thus far. This focal disease occurs in young people as well as in older people. It is found in inflamed appendixes and in the so-called normal appendixes taken out in the course of abdominal operations. It is located in the muscle coat and in the serosa of the appendix. In the fallopian tube, it has been found in the outer layers only. I have not seen it in any other organ of the body except, perhaps, in one subacutely inflamed inguinal lymph node.

The similarity of the lesion to that of small arteries in periarteritis nodosa is striking. Some of my own photomicrographs could almost be substituted for the pictures that Dr. Olcott showed tonight.

The distribution of the lesion is very irregular. It generally occupies only small parts of an arteriole. By making serial sections and reconstructing, one finds that, for instance, one small branch of an arteriole may be involved for a distance of a fraction of a millimeter, being normal above and below that point, and with all other branches in the same region being normal.

Thus it is easily understood that no disturbance of the tissue due to the closure of these small vessels can be found. Theoretically, however, I consider this lesion of great importance. Since it is found in tissues removed from all kinds of patients without relation to any specific infection and without relation to age, the best way out of our ignorance may be to surmise that some immunologic condition of the tissues may be responsible for the pathologic change in the arterioles.

The lesion always seems to begin with a hyaline deposit under the endothelium. The difficulty of having a distinctly focal disease caused by an immunologic change certainly exists. Our hypothesis shares that fault with many others.

It seemed to me incredible that a characteristic morphologic change in the vermiform appendix requiring no special methods for finding it should have escaped detection so far. I therefore have hesitated to come forward with it.

FACTORS INFLUENCING ERYTHROCYTIC SEDIMENTATION. THOMAS H. CHERRY and (by invitation) JOHN A. KILLIAN.

The tables presented show that there are two factors that apparently influence the rate of sedimentation. The first is the physical and visible elements; the cross-sedimentation experiments indicate that elements in the plasma definitely influence the rate. The cell volume and total solids indicate that the smaller the volume and the diminution in solids the faster is the rate of sedimentation. The second factor is the chemical one. An increase in the sugar concentration diminishes the rate of slow sedimentation, and has no effect on the rate of fast sedimentation. The total protein remains unchanged. Variations in the protein fractions, however, accompany changes in the rate of sedimentation. Fibrinogen or fibrin is relatively increased in the fast, and decreased in the slow, blood. The surface tension is relatively increased in the fast, and decreased in the slow, blood. Globulin in the fast blood is relatively high in the form of euglobulin. In the slow blood, the globulin fraction is relatively decreased. Changes in albumin are the reverse; that is, the fast blood shows diminished, and the slow increased, albumin. Thus the increase in albumin compensates for the changes in the globulin fractions.

DISCUSSION

JOHN A. KILLIAN: The conspicuous feature of these experiments, it seems to me, is this: When you take the red blood cells from blood that has a fast rate of sedimentation, centrifugate them off, wash them in physiologic solution of sodium chloride, and suspend them in the plasma of blood that has a slow rate of sedimentation, their speed of sedimentation is greatly increased; in other words, it is put in the range that is considered normal. On the other hand, if you take the red cells from normal blood, centrifugate them off, wash them and suspend them in the plasma of blood that has a fast rate of sedimentation, these cells sediment rapidly, so that they are then in the range that we consider to be pathologic. In the preliminary studies on the influence of centrifugating and washing the red cells with physiologic solution of sodium chloride on the rate of sedimentation the cells in their own plasma, it was observed that apparently these two processes have little effect. These experiments seemed to indicate that the factors that influence the rate of sedimentation of the red cells are in the blood plasma. However, this does not appear to be the entire explanation, for in the case of secondary anemia showing no leukocytosis and a fast rate of sedimentation of the red cells, there is a definite change in the total solids of the blood and in the red cell volume. Of course, the change in the total solids of the whole blood may be associated with a change in the red cell volume. It becomes a more and more complex problem to explain the factors that influence the rate of sedimentation, and so far, I think, the only indication we have of the nature of these factors is from this cross-sedimentation experiment. The results for surface tension are suggestive, but what they mean I do not know. In an association of two phenomena of this kind, the fast rate of sedimentation and the increased surface tension, the question arises: Which is the cause and which is the effect? I do not think we can conclude that the changes in the surface tension of the plasma are necessarily associated with the rate of sedimentation in the nature of cause and effect.

One important finding made in seventy-five analyses of blood, representing a wide range of pathologic conditions, was that the total serum protein in each case was well within normal limits. Considerable variations were noted in the fractions, particularly in globulin, as compared with the albumin, fraction. The variations

in the globulin fraction were always found in the euglobulin, and not in the pseudoglobulin, but these appeared to be always compensated for by the inverse variations in the albumin fraction.

ARTHUR F. COCA: The speakers have not mentioned the blood groups, which we are especially interested in. I wonder whether the plasma with which these cells were mixed was from persons from the same blood group.

JOHN A. KILLIAN: Yes.

PRECIPITATION TESTS FOR SYPHILIS. HARRY EAGLE (by invitation).

Fundamentally, all the precipitation tests now used for the diagnosis of syphilis are identical. An alcoholic extract of mammalian tissue is diluted with some sort of aqueous solution, forming a suspension of lipoid particles. These have little tendency to cohere, and remain discrete when added to normal human serum. In syphilitic serum, however, they combine with a reactive substance (reagin), which forms sensitizing films of denatured protein around the individual lipoid particles. When the stabilizing surface charge on these films is reduced below a critical level, as it is by dilute electrolyte, these charged films fail to repel each other, and the particles cohere on impact.

Despite this underlying identity, the tests now in use differ materially. The points of difference fall into two general categories: (1) those that affect the properties of the lipoid suspension used as antigen and (2) those that affect the aggregration of the lipoid-reagin compound. In the first group belong such factors as the source of the lipoid, the method of purification, the method of extraction, the materials used for sensitizing the antigen, the lipoid; the quantity of salt solution used to dilute and its concentration, the method of dilution, etc. To the second group belong such factors as the antigen-serum ratio, the duration of shaking, the duration and the temperature of incubation, the total volume, the method of reading, etc. These variables adequately describe every precipitation test now in use.

In general, the best of the precipitation tests are more sensitive than the best of the Wassermann technics. Their fault lies in the difficulty of reading weak positive reactions. The indefinite character of the aggregation in such cases calls for close reading, and this in turn makes for the reporting of false positive reactions. Improvement in the precipitation tests can be expected along three lines. In the first place, the optimum values of the variables listed in the foregoing paragraph can be determined on both theoretical and empirical grounds; the application of these optimum values in the precipitation test will necessarily result in greater sensitivity and more clearcut results. In the second place, new sensitizing substances will be used to replace or supplement cholesterol. The greater sensitivity of a cholesterolized antigen is due to the fact that the cholesterol forms myriads of microscopic and submicroscopic particles that adsorb the active lipoid. The visible result is an increased opacity, due to the presence of many more microscopically visible particles. The coarsened dispersion facilitates aggregation; moreover, the complex lipoid-cholesterol particles have an unexplained greater avidity for reagin. Since the sensitizing action of cholesterol is due solely to its physical properties, any substance with similar physical properties can be expected to have a similar sensitizing action. This has been found to be the case. The use of two other sterols, derived from corn germ and wool, as adjuncts to cholesterol, has resulted in a significant increase in the size of the aggregates formed, and thus, in the sensitivity and clarity of the results. Finally, insufficient use has been made of the centrifuge as a means of facilitating aggregation.

Eventually the precipitation phenomenon will probably supplant the fixation technic as the diagnostic criterion for syphilis, but not until some method has been found for increasing the sensitivity of precipitation tests with spinal fluid. Even the most sensitive precipitation tests now available are inferior to the Wassermann test with large quantities of spinal fluid, and until this difficulty has been successfully overcome, the Wassermann test cannot be considered, as it is by some serologists, an anachronism.

DISCUSSION

WARD J. MACNEAL: I wish to congratulate Dr. Eagle and to express my pleasure at listening to his description, which is of course fragmentary, of the large amount of work that he has done in an attempt to put this reaction on a more precise and scientific basis than it has been. Some ten or fifteen years ago there were serologists who felt that the last word had been spoken about the serologic tests for syphilis, or, at least, that the last word ought to have been spoken. However, I think that those who have had to deal practically with the problem have not shared this opinion. The serologic tests for syphilis are of the greatest value in the handling of this important disease. I believe that a matter that is so important practically, requires continuous study, and certainly offers opportunities for obtaining more exact knowledge than we possess at the present time.

The attitude of the clinician toward laboratory work in syphilis deserves some general remarks. I recall my professor in syphilology stating thirty years ago that syphilis is one disease in which the laboratory has nothing to offer, and that it is a disease in which the clinician needs no help from the laboratory, because the clinical evidence is so clearcut and definite that a physician can recognize the disease when it exists. There has been a remarkable transformation in the attitude of the syphilologists in the last thirty years, for now, at least in this city, one finds that the case of a syphilitic patient is sometimes briefly recorded as "Wassermann ++++" or "Kahn ++++." There is little record of the tale of woe and practically no record of a physical examination on the part of the physician. The syphilologists of thirty years ago would probably turn over in their graves if they should see the way in which a case of syphilis is handled and the emphasis that is placed on the laboratory tests. Those of us who perform the tests have much less confidence in them than many of the clinicians who receive the reports. They seem to take that "4" as being the last word in the recognition of syphilis, and I think that the laboratory men who see the other side sometimes have great doubts. I have gone over histories and have become convinced that occasionally the patient is being treated for having a figure 4 on a sheet of paper, rather than for any form of disease that exists in him. Undoubtedly there are errors of this sort that are rather tragic for the patient.

I have been interested in following the work that Dr. Eagle has done, and I am sure that new light has been thrown on this problem by him. However, any new technical procedure has to pass the test of application to a considerable number of cases. I should like to see the statistics divided into three groups instead of two, the first group to include statistics from the application of the test to persons in whom there is no suspicion of the existence of syphilis; the second group, those from its application to persons who are known to have syphilis, but who have not been treated for this disease for a considerable period of time, and the third group, those from application of the test to syphilitic patients under treatment. Unfortunately, one is able to get a large number of data of the first and the third groups, but it is not so easy to get a large number on persons who are known to be syphilitic, but who have been without medication for a long time. Syphilitic patients under treatment are the ones, in my own observations, who have shown the greatest serologic discord. On that account, I feel that several different tests ought to be employed for syphilitic patients under treatment, so as to indicate to the clinician in charge of the case that there still remains in the blood of the patient something that makes it different from the blood of a person who has not had syphilis. Even though some of these tests are wholly incapable of detecting that difference, some of the other tests detect it. In my opinion, the blood of a syphilitic person who gives a positive reaction with any one of these tests should be regarded as showing evidence of syphilitic disease. However, there are syphilographers who do not take this view, and who are willing to believe that a patient with a negative reaction in some one test has been relieved of his infection.

ARTHUR F. COCA: I have not much to add to what Dr. MacNeal has said. I agree with him in general and in detail. When he said that in the old days the clinicians did not need the laboratory in order to make a diagnosis of syphilis, he could have added that in some laboratories the technician does not need the clinician to make a diagnosis of syphilis. He pointed out especially the seriousness of the results of the test. It is different in that respect from almost any other clinical test. It is a colloidal reaction or depends on a colloidal reaction which is notoriously uncertain, especially in the zone at the end of the titer, that is, just where we have to make our most difficult readings in the case of syphilis in which treatment has been given or in that of a weak reaction. If one should send a specimen of urine to a dozen laboratories to be tested for the presence of sugar, even one of a urine in which there is only a very small quantity of sugar, there will be hardly any difference of opinion among these laboratories as to the result. But if one sends a serum in which the precipitation is weakly positive, or the serum of a treated syphilitic patient, to different laboratories, the results will be found to be in disagreement in four of five cases. In other words, we are never sure in such specimens of any particular serologic state of the serum.

Finally, I think we ought to remember what Dr. Eagle has said about the difficulty that surrounds the proper performance of precipitation tests. We have to remember in how many laboratories these important tests are in the hands of technicians who have practically no understanding of the fundamental nature of the reactions. I should like to emphasize what Dr. MacNeal has said in one more general point, and that is that any test that is to replace the Wassermann or the precipitation test will have to be tried out on the several categories of syphilitic patients, especially the treated syphilitic patients. Unless the nature of the reaction can be changed considerably, it does not seem to me that there is much hope of there being a test devised that will give the same result on the same serum with different antigens. Take such a simple test as the agglutination test. Many years ago I heard that von Dungern, Neisser and Sachs were testing the same agglutination test, attempting to check one another's results in the final titration. They were unable to do it, although they tried many times; and last year Landsteiner in Paris met with three or four other competent serologists and attempted to titrate the same grouping serum against the same suspension of blood. The results differed as much as eight times in the titer. This inconsistency is a property of all kinds of immunologic reactions, which I have not much hope of our being able to get over.

HARRY EAGLE (closing the discussion): The question which Dr. MacNeal brought up of the so-called $++++$ reaction is interesting. As you know, $++++$ is supposed to mean strongly positive; $+++$, $++$ and $+$, decreasing degrees of positivity, and 0, negative. Actually, the terms do not mean anything of the sort. The degree of positivity of a syphilitic serum can be expressed in the same terms as the titer of a positive Widal serum. If one takes the serum from a patient with active syphilis and does a quantitative Wassermann test by serial twofold dilutions of the serum, one finds that the serum may give a titer as high as 400; that is, diluted 400 times, the serum will still give a positive Wassermann reaction. This is rather unusual, but one gets a few with a titer of 200, and a large number with a titer of 100. In other words, $++++$ does not necessarily mean a strongly positive reaction. It may mean anything from a serum containing one unit to a serum containing 400 units. And since the designation $++++$ does not mean a strongly positive reaction, it should be dropped. The designations $+++$, $++$ and $+$ do not mean decreasing degrees of positivity. They may mean weakly positive reactions, but they may also mean a technical error in the laboratory. It has been recommended by the League of Nations, and the recommendation should be adopted, that in reporting the results the terms "positive" and "negative" or "doubtful" be used. Indefinite aggregation in the precipitation test also calls for a doubtful report, and any such doubtful report calls for a repeated test.

As Dr. MacNeal and Dr. Coca said, it is tragic to label a patient syphilitic because of a single positive reaction. I had rather report fifty false negative reactions than one false positive reaction. I put the ratio even higher, because if the patient learns of the report, no number of negative reactions is going to erase the suspicion that he may have syphilis.

Regarding the incidence of a positive Wassermann reaction in different types of syphilis, we have been much struck by the fact that the incidence of positive serologic reports is much higher than the books give it. In the literature, the incidence of a positive serologic finding ranges from 30 to 100 per cent in the various types of syphilis. In going over our reports for the last fifteen years, we found that the average for all types of syphilis by the icebox Wassermann technic is around 90 per cent. Finally, I think that the precipitation tests can be made to be reliable, but not until the weak positive reactions can be clarified. Until the difference between a weak positive and a negative reaction is unmistakable, all reports of weak positive reactions should be suspected. And it is the laboratory worker himself who should be the most conservative in the interpretation of results.

PATHOLOGICAL SOCIETY OF PHILADELPHIA

Meeting of Dec. 10, 1931

BALDUIN LUCKÉ, *President, in the Chair*

A FOUR-CUSPED PULMONARY VALVE. W. T. READ, JR.

A white woman, aged 31, who died suddenly eleven days following cholecystectomy, had given no evidence in history or in physical examination of cardiac disease, except for slight pretibial edema. At autopsy, marked dilatation of the right side of the heart was found, with a four-cusped pulmonary valve. A brief report of the number of such cases in the literature was given.

BILIARY CIRRHOSIS WITH ATRESIA OF THE EXTERNAL BILE DUCTS AND ABSENCE OF THE SPLEEN. W. T. READ, JR.

A white female infant was studied until her death at the age of 10 months. Jaundice, light-colored stools and dark urine were noted from the fifth week of life on. These symptoms fluctuated but never disappeared. Terminal ascites developed. During life, the infant had bilateral otitis media. At autopsy, a markedly cirrhotic liver of the biliary type was found. The common duct could not be identified, and fibrous remnants of the cystic and hepatic ducts were all that could be demonstrated. The gallbladder was small and fibrous, and contained no bile. A thorough examination of the abdominal cavity revealed no spleen. A chain of nodules was found that, on gross examination, were thought to be, possibly, small splenic nodules. Histologically, these proved to be hyperplastic lymph nodes.

HISTOGENESIS OF ATROPHIC CIRRHOSIS. V. H. MOON.

This article will appear in full in the ARCHIVES.

OBSERVATIONS OF LYMPHATIC CAPILLARIES STUDIED MICROSCOPICALLY IN THE LIVING MAMMAL. E. R. CLARK and E. L. CLARK.

Moving pictures were shown of lymphatic vessels growing in the transparent chamber in the rabbit's ear.

Book Reviews

Intracranial Pyogenic Diseases: A Pathological and Clinical Study of the Pathways of Infection from the Face, the Nasal and Paranasal Air-Cavities. By A. Logan Turner, M.D., LL.D., F.R.S.E., Consulting Surgeon, Ear and Throat Department, Royal Infirmary of Edinburgh, and F. Esmond Reynolds, M.D., D.T.M. & H., M.R.C.P., Superintendent of the Laboratory of the Scottish Asylums' Pathological Scheme. Cloth. Price, 12/6. Pp. 271, with 82 illustrations. Edinburgh: Oliver & Boyd, 1931.

Fatal intracranial infection secondary to an inflammatory focus on the face or in the nasal and paranasal air cavities is not uncommon. Experimental and microscopic investigations have been carried out on the pathways of infection in tuberculosis and epidemic meningitis and in the group of infections of the central nervous system attributed to the filtrable viruses, but in the literature there are few records of a systematic and comprehensive microscopic investigation of the pathways of pyogenic infection of the brain and its membranes from extracranial septic foci. This scholarly treatise is the result of nine years of investigation of this subject. The authors realize the advantage of a close and sympathetic cooperation between the pathologist and the clinician, and throughout the work such a cooperation is evident.

The material for this investigation was obtained from a series of fatal cases of intracranial infection, secondary to an inflammatory focus on the face and in the nasal and paranasal air cavities, and in twenty of the cases an attempt was made to demonstrate by microscopic preparations the actual path by which the infection reached the intracranial structures. In addition to the twenty cases examined in this detailed manner, there is a further group of thirty-five cases, nine of which were studied clinically and twenty-six both clinically and post mortem. The primary septic focus was situated on the face in four cases, in the paranasal air cavities in forty-five cases, in the fauces in one case and in the middle ear cleft in five cases. The secondary involvement included forty-nine cases of intracranial complications and six cases of general blood infection in which no localized intracranial infection was present or at any rate demonstrable at autopsy.

The arrangement and presentation of the material are excellent. After a review of the literature on the subject, the methods employed in the investigation and a tabular statement of certain main facts concerning the fifty-five cases investigated, a general consideration of the pathways of infection of the intracranial structures is presented. The anatomic details necessary for the correct interpretation of the cases are clear and concise. The diagrams, illustrations, photographs and photomicrographs are well chosen. Twenty-two of the microscopic illustrations are in colors. Each of these illustrations is accompanied by a full page explanatory diagram. The cases investigated are grouped to illustrate the common pathways of infection of the intracranial contents. An account of the history of the case, the progress of the infection and the physical and postmortem observations, a brief summary of the bacteriology and a detailed account of the microscopic examination of the tissues in an effort to trace the pathway of the infection are given. The comments on the results of the investigation in each case are logical and conservative. The correlation of the clinical signs with the underlying anatomic change is emphasized.

An analysis of the pathways of infection from the various primary foci shows that the venous blood stream carried the infection in nineteen cases — thirteen of these were of cavernous sinus thrombosis and of general blood infection; that direct extension through the bone was responsible in twenty cases and a combina-

tion of direct extension and blood stream infection in eight and that infection was transmitted along the olfactory perineural sheaths in four. In four cases, none of which was examined microscopically, the pathway could not be determined.

From the evidence presented the authors emphasize that when infection passes by the blood stream from an inflammatory focus on the face or in the nasal or paranasal air cavities to the intracranial structures, the initial infection of cutaneous or mucosal veins gives rise, as a rule, to infective thrombosis of the cavernous sinus.. The pathway of infection in thirteen of the cases was entirely by way of its afferent or efferent venous channels from the face, pharynx, air cavities and middle ear cleft. In eight of the cases the preliminary stage of the infective process was by direct extension through the bone, followed by further spread to the sinus along the osseous veins. In the latter group, the primary focus was in the frontal, ethmoidal or sphenoidal air cavities. Infection of an osseous vein in the wall of the paranasal air cavity or in any of the bones forming the cranial box may give rise to purulent leptomeningitis.

When the process advances by direct extension through the bone and dura, diffuse leptomeningitis is the usual result. In these cases various stages mark the progress of the infective process; these are osteomyelitis with or without an extradural abscess, then pachymeningitis, subdural infection and leptomeningitis. When extension of the inflammatory process passes along the olfactory perineural sheaths, leptomeningitis is set up; at first it is limited to the cribiform plate, but later becomes generalized.

Septicemia and pyemia may develop in cases of osteomyelitis of the cranial bones without intercurrent infection of any of the blood sinuses. Six cases of this type are recorded. In all of them the primary focus was in one of the paranasal air cavities. The complication may arise immediately following an operation on the cavities or spontaneously in the natural course of the disease in these cavities.

No attempt has been made by the authors to investigate the bacteriology of the cases in the series. This is unfortunate. However, certain data have been collected from the routine bacteriologic examination in forty of the cases, and these results are summarized in one chapter. There is an extensive bibliography. No discussion of the treatment is offered. The treatment depends to a great extent on a knowledge of the process in each case and on a careful study of the changes arising in consequence of the particular pathway pursued by the infection. This book will be of interest to all who are concerned with such conditions.

Tumours of the Breast: Their Pathology, Symptoms, Diagnosis and Treatment. By Sir G. Lenthal Cheatle, K.C.B., C.V.O., F.R.C.S., Consulting Surgeon and Emeritus Lecturer on Surgery, King's College Hospital, London; Late Surgeon to and Lecturer on Surgery at King's College Hospital, London; Walker Prizeman, 1926-1930; and Max Cutler, B.Sc., M.D., Director of Tumour Clinic, Michael Reese Hospital, Chicago; Late Clinical Fellow, Memorial Hospital, New York; Director of Research Division of Cancer Department of Hospitals, New York; Attending Radiation Therapist, New York City Cancer Institute. Price, $12. Pp. 596, with 18 colored plates and 468 other illustrations. Philadelphia: J. B. Lippincott Company.

In this comprehensive and competent work the reader will find a veritable mine of information regarding every department of knowledge of the physiology and pathology of the breast, and the specialist will encounter a detailed and expert discussion of all those practical and theoretical problems of diagnosis and treatment which render tumors of the breast a difficult medical specialty. Throughout these pages one detects the broad experience and philosophical attitude of the senior author, aided by the industry and discernment of his younger collaborator. If there is any fault to be found in the work as a whole, it lies in the richness of material available, the freedom with which it is presented and the elaborate discussions and analyses with which the central questions at issue are pursued.

It is no treatise for the beginner, but the specialist in many lines who brings adequate familiarity with him will delight and profit in following the authors to the full limit in their presentations. This task is rendered comparatively easy by a profusion of photographs and colored plates, which present the morphologic side, probably more fully than has ever before been attempted. In this field the great value of sections of the whole breast, by the methods developed by the senior author, is constantly apparent, and the student should not fail to make full use of these impressive reproductions. With the exception of the opening chapters, all the material in this work is new and represents the original observations of the authors.

After an adequate review of the anatomy and embryology of the breast, there follows a valuable summary of data on the interrelations of the breast with the uterus and ovaries through the action of hormones, and some consideration of the use of ovarian extracts in the treatment for mammary diseases.

The various forms of chronic mastitis are regarded as physiologic and functional disturbances, and not as inflammatory. The fibrous form is designated as "desquamative epithelial hyperplasia," and the term "mazoplasia" is introduced. Cystic mastitis is called "cystiphorous desquamative epithelial hyperplasia," and is regarded as an important antecedent of carcinoma. It is emphasized that the essential carcinomatous process begins before there is actual invasion. About 20 per cent of all mammary cancers are found to begin in the lesions of the cystiphorous state. Many will regard this proportion as too low, and inquire how the other 80 per cent begin. The numerous precancerous phases of this condition are fully traced.

Carcinoma of the breast is presented fully from every angle, including histologic stages, grades of malignancy and radiosensitivity, modes of extension, local and general; methods of diagnosis by palpation, transillumination, aspiration and biopsy and methods of treatment by surgery and radiation. Some readers may not be entirely satisfied with the prominence given to the various gross anatomic phases of mammary cancer. The facts are there, but they do not stand out. If this is a fault, it is more than balanced by effective reference to many less common benign and malignant conditions in the breast which are often dismissed too lightly by most writers.

Paget's disease occupies a prominent position in the work, elaborately illustrated and competently discussed from the detailed study of seventeen cases. The view is maintained and adequately supported that Paget's disease is a primary carcinoma of the skin of the nipple, often involving the epithelium of the terminal ducts and frequently, but not always, associated with single or multiple foci of cancer in the deeper duct system. Here and elsewhere the authors acknowledge the aid of the fine technical skill and pathologic interpretation of Dr. J. D. Ludford.

An important section relates to the radiation treatment for mammary cancer, both operable and inoperable. The data on the various phases of this question are rather fully presented and conservatively discussed. While some remarkable results of radiation treatment by various methods are reported, the authors refrain from expressing any definite recommendations and await further progress in this experimental field. A well chosen bibliography follows each chapter.

The publication of a highly specialized work of this character, reflecting the mature experience of many years of study and observation with a large material, emphasizes anew the great complexity and difficulty of the problems of mammary tumors. It explains and justifies the tendency to regard mammary cancer as a field demanding the comprehensive knowledge and wide experience of the specialist, and warns against the assumption that these diseases may be competently handled as a side issue in the work of the general surgeon and radiologist. The authors are congratulated on having achieved this object, among others, by preparing a comprehensive work of permanent value and conveying an impressive message on this most important subject.

Grundriss der Entwicklung der Menschen. By Alfred Fischel. Paper. Price, 11 marks. Pp. 141, with 117 illustrations, in part colored. Berlin: Julius Springer, 1931.

Those facts that every physician should know regarding the development of the human embryo have been selected by Professor Fischel from his large textbook of human embryology and are presented in the "Grundriss" in a greatly condensed and convenient form. The demand for this kind of book is large and arises not only from the needs of the medical profession but also from the requirements of that large group of readers composed of premedical students who have to pass examinations. Several books of similar scope and character have appeared in the English language during the past few years. Professor Fischel, however, has attained a conciseness and clarity that most of the books in English lack, and to those who read German easily his book will have a strong appeal.

It is not an easy task to present, in so few pages, a complicated phenomenon, like the development of the egg and the formation of the organs of the embryo. The success that marks Professor Fischel's effort is in part to be accounted for by the fact that his pen was still moist from the writing of his "Lehrbuch," in which his conceptions and interpretations had been clarified and put down in orderly fashion. It is, of course, this larger work that is the important one and that will always redound to his credit. That such a superb product should evolve from amidst the profound disturbances of the World War is an example of that marvelous attribute of scholarship, the ability of detaching itself from surrounding political and social conditions. It will be remembered that Plato wrote his "Republic" during those same days when the city-states of Greece were blindly tearing each other apart in their bitter political rivalry, and the Academy carried on and produced students of the quality of Aristotle when the annihilation of the Athenian Empire seemed to have sealed the doom of all that was noblest and best in Greek life.

Association française pour l'étude du cancer. Atlas du cancer., Neuvième et dixième fascicules. Les tumeurs des centres nerveux et des nerfs périphériques. By Gustave Roussy and Charles Oberling, from the Foundation of Henri de Rothschild. Paper. Price, 80 francs. Paris: Félix Alcan, 1931.

This beautiful atlas, published by the generosity of Dr. Henri de Rothschild, has been appearing in successive fascicles. The present ninth and tenth fascicles deal with tumors of the nervous system. The illustrations are beautifully clear, as they have been in the other parts of the atlas. It is unfortunate, however, that at present there is a period of anarchy in the terminology of cerebral tumors, which is apt to confuse the uninitiated, although the authors give synonyms for the names they use. It is at any rate evident that the same types of tumors can be traced through all the recent publications concerning gliomas, whatever the terminology used. One has a little difficulty in understanding why the authors have changed oligodendroglioma to "oligodendrocytome." There is also no justification for calling a spongioblastoma an "oligodendrocytome à cellules fusiformes"; the authors offer no proof of any kind of the oligodendroglial nature of the cells of this tumor. The tumor labeled "astrocytome pseudo-papillaire" is the glioma that Bailey has described with Bucy under the name of astroblastoma. The tumor in plate 8, figure *D*, looks much like a tumor of Rathke's pouch. Nobody seems to fancy the term medulloblastoma, which Bailey introduced for the malignant cellular tumor of the cerebellum of children, but "neurospongiome" is no improvement, because it does not take account of the neuroblasts that differentiate in these tumors. With the exceptions noted, the atlas should prove useful to pathologists, especially in French-speaking countries. The histologic atlas on gliomas by Percival Bailey (ARCH. PATH. **4**:871, 1927) covers the same field.

Annals of the Pickett-Thomson Research Laboratory. Volume 6. The Pathogenic Streptococci. The Role of the Streptococci in Scarlet Fever. By David Thomson, O.B.E., M.B., Ch.B. (Edin.), D.P.H. (Camb.), Hon. Director, Pickett-Thomson Research Laboratory, St. Paul's Hospital, London, and Robert Thomson, M.B., ChB. (Edin.), Pathologist to the Pickett-Thomson Research Laboratory. Price, $10. Pp. 470. Baltimore: Williams & Wilkins Company, 1930.

The original plan to devote this volume to summarizing the knowledge about streptococci in erysipelas, skin diseases and scarlet fever had to be abandoned because the material on scarlet fever alone was found to require the whole volume. The succeeding volume of the Annals deals with the streptococci in erysipelas, skin diseases and measles. Like other volumes of the Annals, the volume on streptococci in scarlet fever represents an enormous amount of work. Some 1,400 papers have been abstracted and indexed. "The research work carried out on scarlet fever during the past five years is greater than the whole of the total previous researches on the subject. This great increase of research on scarlet fever in recent years is largely due to the discovery of the Dick toxin and the Dick test, which has led to new methods of investigation." The authors conclude that scarlet fever is caused by a specific streptococcus which, they say, may be justly called Streptococcus scarlatinae. The growing knowledge of the differences between the various pathogenic streptococci is summarized. The index has been prepared with special care in order to make it as helpful as possible. It will save workers much time and effort in hunting for references. As an abstract and catalogue of the literature on streptococci in relation to scarlet fever the volume stands without a rival.

Osler and Other Papers. By William Sydney Thayer, M.D., LL.D., Dr. Hon., ScD., F.R.C.P. Ire.Hon.; Professor Emeritus of Medicine at the Johns Hopkins University. Price, $3.50. Pp. 386. Baltimore: Johns Hopkins Press, 1931.

This book includes twenty-four addresses and papers "delivered or published at intervals during an active professional and university life, comments, for the most part, on men and things medical." The first five chapters are devoted to Osler, with whom the author was associated closely during his period in Baltimore. These chapters give vivid reminiscences of the great master and happy illustrations of his character and influence. There are also brief but stimulating accounts of the life and work of Bright, Laennec, Pasteur and Fitz, as well as tributes to Howland and Welch. Other chapters include: the problems of medicine, teaching and practice, scholarship in medicine, the university and medicine and the duties and problems of the physician. The dominant note in all the chapters is the intense devotion of the author to high ideals. Idealism coupled with an accomplished pen gives the writing charm and power. It is a delightful volume.

Books Received

TUMOURS OF THE BREAST: THEIR PATHOLOGY, SYMPTOMS, DIAGNOSIS AND TREATMENT. By Sir G. Lenthal Cheatle, K.C.B., C.V.O., F.R.C.S., Consulting Surgeon and Emeritus Lecturer on Surgery, King's College Hospital, London; Late Surgeon to and Lecturer on Surgery at King's College Hospital, London; Walker Prizeman, 1926-1930; and Max Cutler, B.Sc., M.D., Director of Tumour Clinic, Michael Reese Hospital, Chicago; Late Clinical Fellow, Memorial Hospital, New York; Director of Research Division of Cancer Department of Hospitals, New York City; Attending Radiation Therapist, New York City Cancer Institute. Price, $12. Pp. 596, with 18 colored plates and 468 other illustrations. Philadelphia: J. B. Lippincott Company.

ROENTGENOLOGIC STUDIES OF EGYPTIAN AND PERUVIAN MUMMIES. By Roy L. Moodie, Paleopathologist to the Wellcome Historical Museum, London. Berthold Laufer, Curator of Anthropology, Editor. Anthropology Memoirs, Field Museum of Natural History Founded by Marshall Field, 1893. Volume 3. Paper. Price, $5. Pp. 66, with 76 plates. Chicago: Field Museum of Natural History, 1931.

THE INTERVERTEBRAL DISCS: OBSERVATIONS ON THEIR NORMAL AND MORBID ANATOMY IN RELATION TO CERTAIN SPINAL DEFORMITIES. By Ormond A. Beadle. Medical Research Council, Special Report Series, No. 161. Price, 2 shillings, net. Pp. 179. London: His Majesty's Stationery Office, 1931.

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